High rates of metal allergy amongst Nuss procedure patients dictate broader pre-operative testing

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Abstract

Purpose: A previous study from our group estimated that as few as 2.2% of pectus excavatum patients suffered from allergy to the implanted metal bar. We sought to assess recent changes in incidence of metal allergy and identify the benefit of metal allergy testing prior to surgery.

Methods: A retrospective review was performed of all consenting patients undergoing pectus repair during the six years between 9/2004 and 12/2010 at our institution. Incidence was based on clinical symptoms and/or T.R.U.E.® patch testing. Demographic data, history of atopy and history of metal allergy were collected. Type and number of bars used, suture site infection, skin rash and wound infection rates were reviewed.

Results: Forty one of 639 patients (6.4%) had clinical or patch test evidence of metal allergy. Family history of metal allergy and pre-operative history of metal sensitivity were found to be statistically significant correlates.

Conclusions: The rate of metal allergy in the pectus excavatum population may be higher than previously reported. Patient or family history of metal allergy or metal sensitization may indicate increased risk. Metal allergy testing should be performed before Nuss procedure.

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The use of metal implantable devices is common. Metal implants may provide a scaffold, as in the use of plates and screws to stabilize broken bones, or they may replace non-functioning body parts, as in joint replacement. In some cases, metal implants allow minimal disruption of native tissues with results as good as, or better than, operations with significant tissue impact. Pectus excavatum is one such deformity that has benefited from the use of a metal prosthesis to allow for minimally invasive repair.

The Nuss procedure has become the predominant reason for the use of metal implants by pediatric general and thoracic surgeons [1]. The procedure involves substernal placement of one or more metal bars custom-fitted to a patient’s chest. The bars are secured and left in place for a minimum of two years, after which they are removed.

Stainless steel bars have been used for correction of pectus excavatum since the development of the Nuss procedure in the late 1980’s. However, because of the increased incidence of non-infectious wound complications in patients with implanted stainless steel bars over a 15 year period, we undertook analysis of our database to search for an explanation. Our 2007 report of an eighteen year experience with the Nuss procedure concluded that the rate of nickel allergy in this population was 2.2% [2]. Because the reported incidence of metal allergy in the general population is even higher, at 10% to 15%, we subsequently initiated a screening process for metal allergy [3,4]. Here we report the result of our experience since that time.

The purpose of this study is to determine whether the incidence of metal allergy has increased in our population, whether there are clinical symptoms that suggest metal allergy, and whether it would be beneficial for all patients receiving metal implants to undergo routine allergy testing.

1. Methods

A retrospective review was undertaken for all consenting patients undergoing the Nuss procedure at Children’s Hospital of The King’s Daughters in Norfolk, Va. during the 6 3/12 years between September 1, 2004 and December 31, 2010. In all patients a detailed personal or family history of allergic reactions to metals or jewelry, environmental allergies, eczema and asthma was taken to screen for metal allergy. Only those patients who had a positive screen underwent patch testing with the Thin-layer Rapid Use Epicutaneous patch (T.R.U.E.®) test. The T.R.U.E.® patch test identifies sensitivity to nickel and chromium, but not the other elements of stainless steel. During this period, the T.R.U.E.® patch was variously applied by the nurses in the...
surgical clinic, by the patient’s primary care doctor, or in some cases by a dermatologist or allergist. The overwhelming majority of the interpretations regarding positivity were done by other than dermatology or allergy specialists. Final readings were done at 72 h to be classified as either positive or negative. Patch testing was carried out according to the product information insert of the T.R.U.E.® Patch TEST. Positive reactions were interpreted as outlined in the PI, and are consistent with the standardized guidelines of the ICDS:

Weak positive (+) erythema, infiltration, discrete palpable papules
Strong positive (++) erythema, papules, discrete vesicles
Extreme positive (+++) coalescing vesicles, bullous reaction

Data were not recorded regarding the degree of positivity or the time course of reaction to the metal. The test was regarded as binary, either positive or negative. If T.R.U.E.® patch testing was positive, titanium bars were placed at operation. In some patients, titanium bars were placed for clinical concern, including for history of environmental allergies, eczema, or asthma, but without patch testing.

Data collected included: age, gender, personal or family history of metal allergy, history of environmental allergies, previous Ravitch or Nuss operations, history of asthma or albuterol use, eczema, food or drug allergy, and preoperative history of metal sensitivity. Operative information included age at time of surgery, number of bars placed, type of bar used, suture site infection, skin rash, wound infection, and T.R.U.E.® test patch results if available.

Patients who developed rash, edema, pain, tenderness, or serous drainage with negative cultures for microorganisms were judged to have allergy to the bar after operation even if patch testing was negative postoperatively. Every effort was made to exclude the presence of infection before judging that a patient was allergic to metal. Treatment was continued until resolution of symptoms and normalization of inflammatory markers, or until bar removal at 24–36 months post Nuss procedure.

Statistical analysis was performed using commercially available statistics software with the alpha value set at 0.05 for significance. Fisher’s exact test was used to analyze categorical data while the Student’s T-test was used for numerical data.

2. Results

Between September 2004 and December 2010, 639 patients underwent the Nuss procedure at our facility. Of these patients, 41 (6.4%) were found by patch testing or clinical symptoms to have metal allergy (Table 1). All 26 patients with positive preoperative T.R.U.E.® test underwent placement of a titanium bar. One of these was patch tested to silver in addition, and was allergic to silver. Though silver is not a significant component of the 318 stainless steel, a titanium bar was placed as a precaution. Another 11 patients underwent placement of titanium bars for concern about risk of allergy because of their history alone. These patients did not undergo patch testing, and are not included in patients labeled “allergic”. However, a total of 52 or 8.1% of our patients had alteration in their care because of concern for metal allergy.

Fifteen patients who had negative preoperative history screening were found to be metal allergic post operation. Of these, 10 were positive by T.R.U.E.® patch, and 5 by clinical criteria. There was a single patient who had a negative preoperative T.R.U.E.® test which became positive to nickel post operation. No patient in the allergic group was found to have wound infection. Wound infection was noted in 1.3% of the other patients. A rash was noted in 6 of the 15 patients after operation in the allergic group. Although they gave no history to suggest metal allergy preoperatively, all were positive by T.R.U.E.® patch performed after operation due to allergic symptoms. Rash was noted in 27 (5%) of patients that were not metal allergic. Family history of metal allergy and preoperative history of metal sensitivity were found to correlate with subsequent metal allergy. However, a history of previous repair of pectus excavatum, environmental allergies, asthma or albuterol use, food allergy, eczema and drug allergy was not predictive. Girls were more likely to be allergic than boys (13% vs. 5%) (Table 2).

Eighty-five (85) patients had pre-operative or post-operative T.R.U.E.® patch testing. There were a total of 36 positive tests (26 preop positive and 10 postop). Of these patients, 32 tested positive for nickel, 1 to both nickel and chromium and 1 to both nickel and copper. Two patients tested positive to cobalt, and no one tested positive to gold – 2 metals also tested in the T.R.U.E.® patch testing. All patients were successfully treated until either resolution of symptoms or scheduled bar removal. Treatment for metal allergy included administration of anti-inflammatory medications, usually including steroids. Usually a short course of oral steroids was sufficient, but some patients required long-term administration. Most patients were also administered antibiotics when the redness, swelling, pain and tenderness occurred. No patient needed to have a stainless steel bar removed and replaced with titanium in this group of patients, though that was necessary in two patients in our 2007 report.

3. Discussion

Our previous study indicated a metal allergy rate of 2.2% in patients undergoing minimally invasive pectus excavatum repair [1]. We had originally only performed allergy testing in those patients who demonstrated a personal or family history of metal allergy, eczema, or atopic history. Since that time, our practice has seen an increase in titanium bar usage as well as postoperative diagnoses of metal allergy which prompted re-evaluation of our patient population for metal allergy.

### Table 1

<table>
<thead>
<tr>
<th>Metal allergic patients (41)</th>
<th>Incidence of bar allergy was based on symptoms consistent with metal allergy post-operatively, and/or T.R.U.E. (Thin layer Rapid Use Epicutaneous) patch testing positivity pre- or post-operatively</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received stainless steel bars (15)</td>
<td>post-op positive patch test (10) post-op positive allergic incident diagnosed with pre-op patch test negative (1) unknown post-op patch test results with clinical diagnosis (4)</td>
</tr>
<tr>
<td>Received titanium bars (26)</td>
<td>pre-op patch test positive (26)</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Metal allergic (41)</th>
<th>Non-metal allergic (587)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (5–31 years)</td>
<td>16.1 ± 4.36</td>
<td>16.3 ± 4.36</td>
<td>0.78</td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (521)</td>
<td>27 (65.9%)</td>
<td>494 (84.2%)</td>
<td>0.0027*</td>
</tr>
<tr>
<td>Female (107)</td>
<td>14 (34.1%)</td>
<td>93 (15.8%)</td>
<td>0.0027*</td>
</tr>
<tr>
<td>Family hx of metal allergy (20)</td>
<td>4 (9.8%)</td>
<td>16 (2.7%)</td>
<td>0.0123*</td>
</tr>
<tr>
<td>Hx of Pre-op metal sensitivity (24)</td>
<td>13 (31.7%)</td>
<td>11 (1.9%)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Environmental allergies (265)</td>
<td>12 (29.3%)</td>
<td>253 (43.1%)</td>
<td>0.0842 NS</td>
</tr>
<tr>
<td>Eczema (12)</td>
<td>2 (4.9%)</td>
<td>10 (1.7%)</td>
<td>0.1482 NS</td>
</tr>
<tr>
<td>Previous repair (39)</td>
<td>4 (9.8%)</td>
<td>35 (5.9%)</td>
<td>0.3155 NS</td>
</tr>
<tr>
<td>Asthma or history of albuterol use (175)</td>
<td>7 (17.1%)</td>
<td>168 (28.6%)</td>
<td>0.1127 NS</td>
</tr>
<tr>
<td>Drugs (122)</td>
<td>12 (29.2%)</td>
<td>110 (18.7%)</td>
<td>0.1006 NS</td>
</tr>
<tr>
<td>Food (43)</td>
<td>2 (4.9%)</td>
<td>41 (7.0%)</td>
<td>0.6073 NS</td>
</tr>
</tbody>
</table>

* P value = <0.05 significance level.
The exact prevalence of nickel hypersensitivity in the United States is not known, but it is felt to be increasing since the 1980's [5]. In Europe, legislation has been passed regulating the nickel content of costume jewelry in an effort to stem the continued rise of nickel allergy [6]. Today surgeons must be aware of symptoms exhibited by a patient with metal allergy after metal prostheses have been placed. Nickel allergy has the ability to trigger a complex proinflammatory state [7], in many ways similar to that of sepsis. Local dermatitis, edema, lymphadenopathy [8], recurrent infections [9] and poor wound healing [10] are common manifestations.

Metal contact allergy (a Type IV delayed hypersensitivity reaction) occurs when haptons of the offending agent combine with endogenous proteins which are then internalized by Langerhans cells. These cells subsequently migrate to regional lymph nodes, interact with T cells to create effector cells which will produce an inflammatory response when the host encounters the offending hapten again [11]. In addition, patients can become sensitized to nickel after placement of the stainless steel bar. We encountered this clinically in one patient who initially tested negative via patch test prior to operation but presented with symptoms of nickel allergy.

All metal implants are known to corrode in a biological environment [10], which can lead to adverse consequences depending on their physiologic use. Complications such as joint loosening, in-stent restenosis, wound infection, poor wound healing, chronic inflammation and systemic dermatitis can occur. Due to the relatively short period of time (in comparison to prosthetics used in orthopedics) that Nuss bars are left in place, implant failure is unlikely. However, metal allergy in this population can present with systemic signs of dermatitis [8], masquerade as wound infections, or require repeat surgery for bar replacement as reported previously by our group [2].

Even with aggressive history prescreening, there are patients who develop allergic symptoms. Patch testing is intended to minimize this occurrence. The T.R.U.E.® patch test contains 23 allergens and allergen mixes that have been reported to be responsible for up to 80% of allergic contact dermatitis [12]. Nickel and chromium, elements with the highest concentration in the Nuss bar, are a part of this dermal patch test. In this report, we note that the T.R.U.E.® patch test yielded a false negative result. This has prompted our exploration of the allergEAZE® dermal patch test which includes testing for minor components of the stainless steel bar such as copper, molybdenum, and manganese, while still testing nickel and chromium. Although no dermal patch test presently screens for all components of the steel, a more complete screening process can be used to minimize the risk of a postop allergic event.

When symptoms of metal allergy are encountered postoperatively, medical treatment is usually effective, and stainless steel bar removal or exchange with titanium bars is not generally necessary. A postoperative allergic reaction should be suspected when a patient experiences pain out of proportion to what is expected, unexpected pleural or pericardial effusion, or a non-healing culture negative wound or rash even if dermal patch testing was negative preoperatively. We use the following algorithm for anyone suspected of having a postoperative allergic reaction:

1. Repeat the dermal patch test — patients must be off oral corticosteroids for at least 2 weeks prior to testing. Topical corticosteroids should be stopped at least 7 days prior.

2. If the dermal patch test is positive or if the patient continues to have allergic symptoms a course of nonsteroidal anti-inflammatory drugs followed by oral steroids has been helpful in relieving symptoms. We have been able to preserve the bar with repeated courses of oral steroids.

3. If all attempts at preserving the bar fail, the subsequent clinical decision is to either remove the bar or exchange the bar with a titanium bar. If a bar needs to be removed prior to 2 years, a higher incidence of pectus recurrence is to be expected. Exchanging stainless steel for titanium should be treated as a recurrent pectus repair with all the inherent risks and morbidity associated with a redo repair [13].

The clinical significance of an allergic reaction should not be underestimated. Patients may have significant pain, limitation of activity, delayed wound healing, and delay in return to school and work. Some wound issues require repeat hospitalization and return trips to the OR for wound care. These complications highlight the need for broadening preoperative allergy testing to ensure the proper bar is selected at the index operation.

While the idea of using only titanium bars in all patients may be attractive, there are a number of drawbacks to this approach. Because titanium is less malleable than stainless steel, a titanium bar must be bent using a proprietary computer assisted manufacturing technique to fit the patient's CT or MRI scan. The surface of the bar must be polished to a mirror finish to prevent tissue ingrowth; this is not necessary for the stainless steel bars. Modification of titanium bars during operation is difficult. Lastly, as a result of the above complexities of manufacturing, titanium bars cost roughly four times as much as a stainless steel bar. In our practice, where multiple bars are utilized frequently, this yields a dramatic increase in operative costs. As opposed to the stainless steel bar, the titanium bar is a custom made implant in the United States. If a patient expected to need two bars only requires a single bar, the second titanium bar which was not used cannot be returned to the manufacturer for use by another patient. This increases expense to the hospital. In an era of responsible medical cost containment, it makes sense to use a less expensive but equally effective product particularly when fewer than 10% of patients need the more expensive device. Furthermore, titanium usage does not preclude allergic responses since case reports of titanium allergy in other settings do exist [14]. Though not measured in this study, the cost of treatment of postoperative allergic symptoms in patients is very likely greater than the cost of screening everyone preoperatively.

4. Conclusion

With an aggressive screening process for metal allergies, we discovered that our rate of metal allergy is much higher than identified by our previous report. The incidence at our institution is almost three times what we previously described for true metal allergies, and almost four times higher for concerns of metal allergy. This approaches the incidence in the orthopedic literature [3,4]. Because of the serious morbidity of allergic reaction, including potential additional surgery for bar removal or replacement, we perform dermal patch testing on all patients before Nuss procedure. It is important to counsel families that commercially available dermal patch tests do not test for all components of the stainless bar and a few allergic reactions may be missed. To minimize our false negative rates, we now use the allergEAZE® dermal patch test which includes testing for some of the minor components found in the stainless bar.

References


