SCIENTIFIC ARTICLE

Controversies in Poland Syndrome: Alternative Diagnoses in Patients With Congenital Pectoral Muscle Deficiency

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Purpose Poland syndrome was first described as a deficiency of the pectoral muscle with ipsilateral symbrachydactyly. Currently, numerous case reports describe variations of Poland syndrome in which pectoral muscle deficiency is often used as the only defining criterion. However, more syndromes can present with pectoral muscle deficiency. The aim of this review is to illustrate the diversity of the phenotypic spectrum of Poland syndrome and to create more awareness for alternative diagnoses in pectoral muscle deficiency.

Methods A systematic literature search was performed. Articles containing phenotypical descriptions of Poland syndrome were included. Data extraction included number of patients, sex, familial occurrence, and the definition of Poland syndrome used. In addition, hand deformities, thoracic deformities, and other deformities in each patient were recorded. Alternative syndrome diagnoses were identified in patients with a combination of hand, thorax, and other deformities.

Results One hundred-and-thirty-six articles were included, describing 627 patients. Ten different definitions of Poland syndrome were utilized. In 58% of the cases, an upper extremity deformity was found and 43% of the cases had an associated deformity. Classic Poland syndrome was seen in 29%. Fifty-seven percent of the patients with a pectoral malformation, a hand malformation, and another deformity had at least 1feature that matched an alternative syndrome.

Conclusions Pectoral muscle hypoplasia is not distinctive for Poland syndrome alone but is also present in syndromes with other associated anomalies with a recognized genetic cause. Therefore, in patients with an atypical phenotype, we recommend considering other diagnoses and/or syndromes before diagnosing a patient with Poland syndrome. This can prevent diagnostic and prognostic errors.

Clinical relevance Differentiating Poland syndrome from the alternative diagnoses has serious consequences for the patient and their family in terms of inheritance and possible related anomalies. *(J Hand Surg Am. 2017;■(■):1.e1-e14. Copyright © 2017 by the American Society for Surgery of the Hand. All rights reserved.)*

Key words Congenital upper limb anomalies, differential diagnoses, Poland syndrome.

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The use of the term "Poland syndrome" has a long, controversial history in the literature. In 1841, Alfred Poland[1] described a cadaver with deficiency of the pectoral muscles and ipsilateral symbrachydactyly. In 1895, Thomson was the first to document that syndactyly and deficiency of the pectoral muscles often accompany each other, which led to the suggestion of a new syndrome by Furst in 1900, characterized by deficiency of the pectoral muscles and ipsilateral syndactyly.[2] Two years later, Bing was the first to publish a case series of patients with deficiency of the pectoral muscles and syndactyly.[3] Nevertheless, it was 60 years later that Poland's name was used by Clarkson, a plastic and hand surgeon, as an eponym for the combination of deficiency of the pectoral muscle and syndactyly (Poland syndactyly).[2] Unfortunately, the original phenotypic description of the patient of Alfred Poland was thereby abandoned. Subsequently, "Poland syndactyly" was transformed into "Poland syndrome" and its equivalents "Poland sequence" and "Poland anomaly." These terms have been used in the scientific literature ever since[2].

Currently, the eponym "Poland syndrome" has become a universal term for clinicians to describe all disturbances of pectoral development, with or without symbrachydactyly. This is illustrated by Yiyit et al[4] who reported 113 patients with Poland syndrome of whom only 25 had various upper limb anomalies. Moreover, Catena et al[5] described 8 different types of hand anomalies related to Poland syndrome. The diversity of these reports raises the question of whether Poland syndrome is 1 entity or a group of separate subentities sharing only 1 phenotypic feature, namely pectoral deficiency.

Poland syndrome is not the only syndrome in which disturbances of pectoral development can be observed. For example, Holt-Oram and Duane radial-ray syndrome both can present with absence of the pectoral major muscle together with upper limb anomalies.[6,7] Misdiagnosing patients with pectoral muscle deficiencies as Poland syndrome instead of 1 of the alternative diagnoses might lead to false assumptions about etiology, resulting in a failure to identify associated anomalies or genetic diagnoses.

To create more awareness of the alternative diagnoses in patients with pectoral muscle deficiency, we sought to illustrate the phenotypical spectrum of Poland syndrome in the literature by conducting a systematic review on its presentation. From this review, we identified all atypical Poland cases and defined the phenotypic features that should alert the clinician for a possible alternative diagnosis. We hypothesized that the incorrect use of the eponym Poland syndrome might result in misdiagnosis of some patients.

METHODS

For this systematic review, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed and the checklist is available in the online supplements to this article (Appendix A; available on the *Journal*'s Web site at www.jhandsurg.org). The systematic review protocol was registered in PROSPERO (CRD42015016679).

Search strategy

Seven different databases (Embase, Medline [OvidSP], Web-of-science, Scopus, Pubmed publisher, Cochrane, and Google scholar) were searched for eligible articles. The search strategies used are listed in Appendix B (available on the *Journal*'s Web site at www.jhandsurg.org) and the search was performed in May 2015. Original research articles and case reports containing a phenotypical description of Poland syndrome in the Dutch or English language were included. Articles exclusively about treatment or surgery in Poland syndrome, Möbius syndrome, and general thoracic deformities were excluded. Moreover, reviews, letters to the editor, and articles not available in full text in the medical library of the Erasmus University Medical Center, were also excluded.

Inclusion of articles was done by at least 2 out of 3 reviewers (M.B., E.B.B., and D.S.) and was based on screening of title and abstract. All differences between reviewers in the selection of articles were resolved by consensus. A subsequent exclusion of articles was done during full-text reading, when articles did not fulfill the inclusion criteria.

Data-extraction

Two reviewers (M.B. and E.B.B.) independently extracted data regarding study characteristics and outcomes with the use of a standardized extraction table. The included studies were scored based on number of patients, sex, familial cases, and side of deformity. Furthermore, journal type, definition of Poland syndrome used in the paper, and causal hypothesis supported by the authors were extracted from the articles. A second database was created that included all separate patients described in the included studies. Specific hand and thoracic deformities were extracted, together with other reported anomalies and genetic outcomes. Other reported anomalies were classified in groups by cardiovascular, respiratory,

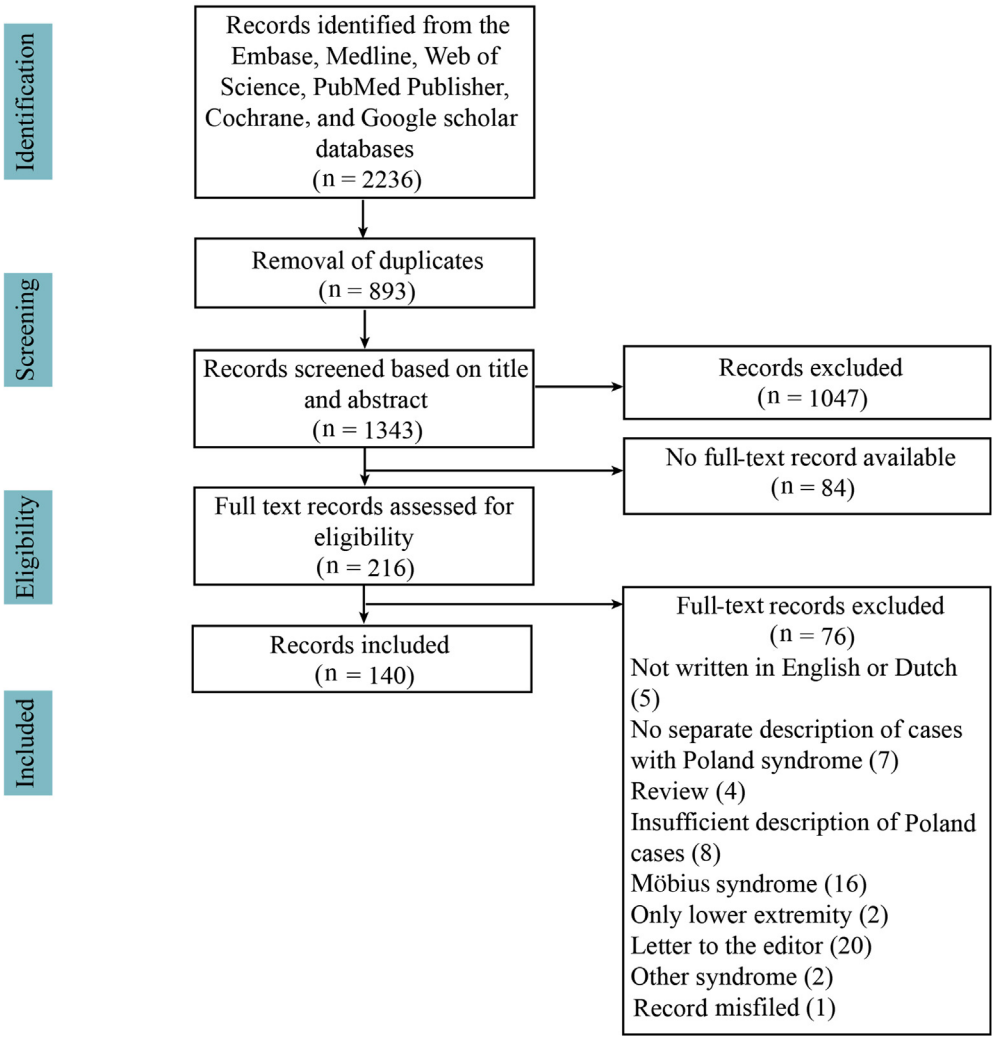

FIGURE 1: Flow chart illustrates all studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage of the process.

urogenital, gastroenteral, vertebral, neurological, craniofacial, dermatological, oncological, and other anomalies. Classic Poland cases, defined by a pectoral major muscle deficiency and ipsilateral symbrachydactyly, were also registered.

Alternative diagnoses

All syndromes with pectoral muscle involvement were extracted from the Human Phenotype Ontology (HPO) dataset.[8] The accession date and search terms are stated in Appendix B (available on the *Journal*'s Web site at www.jhandsurg.org). The extracted syndromes were manually reviewed in the Online Mendelian Inheritance in Man (OMIM) database[9] to confirm pectoral muscle involvement combined with a hand anomaly. Furthermore, all other phenotypic characteristics of these syndromes were extracted from the OMIM database.

To evaluate whether the cases from the literature could fit an alternative diagnosis, cases with a combination of a pectoral malformation, a hand malformation, and an associated anomaly were selected. The selected cases were manually reviewed by the authors to check if any of the observed anomalies were concordant with an alternative diagnosis. The most commonly observed phenotypes that could be related to an alternative diagnosis were summarized.

RESULTS

Literature search results

Out of 1,343 individual records returned by the initial search, 140 records describing a total of 948 patients were included[3–5,10–146] (Fig. 1). However, 6 different studies included in this review described 2 overlapping patient populations, which was confirmed by the

TABLE 1. Different Definitions of Poland Syndrome Used by the Authors of the Included Articles

Definition	n	Percentage	References
1. Major/minor pectoral muscle deficiency/aplasia	110	81	
a. With symbrachydactyly (classical definition)	27	20	3, 15, 17, 18, 28, 35, 53-55, 57, 58, 60, 69, 74, 78, 84, 88, 89, 92, 94, 98, 115, 116, 124, 130, 131, 141
b. With any upper extremity deformity	30	22	13, 19, 21, 23, 24, 30, 32-34, 36, 39, 43, 48, 50, 67, 76, 77, 83, 85, 87, 99, 101, 103, 106, 110, 120, 132, 138, 142
c. With any hand deformity	19	14	4, 14, 16, 44, 56, 63, 66, 72, 73, 80, 81, 91, 93, 111, 128, 134, 140, 147
d. With optional upper extremity deformity	11	8	5, 40, 41, 59, 112, 117, 119, 123, 129, 136, 139
e. With syndactyly	11	8	20, 38, 42, 49, 52, 64, 79, 90, 114, 125, 126
f. With optional hand deformity	5	4	11, 61, 95, 107, 108
g. With optional symbrachydactyly	4	3	62, 71, 133, 146
h. With optional syndactyly	3	2	47, 70, 96
2. Only major/minor pectoral muscle deficiency/aplasia	9	7	12, 29, 45, 46, 82, 100, 113, 122, 127
3. Chest defects	2	1	31, 121
Number of studies with a definition	121	89	
Total number of studies	136	100	

TABLE 2. Observed Thorax Deformities in the Presented Cases Derived From the Included Articles

Description of chest deformity	n	Percentage
Major pectoral muscle agenesis or hypoplasia with optional minor pectoral muscle involvement*	577	99
Areola or nipple hypoplasia or deformity	246	42
Breast agenesis or hypoplasia	112	19
Agenesis or hypoplasia of other muscles	108	19
Rib deformities	106	18
Sternal deformities	72	12
Vertebral deformities	60	10
Scapula deformities	11	2
Abnormal diaphragm	3	0.5
Total number of clinically investigated chest deformities	**582**	**100**

*Patients can have multiple thorax deformities.

authors.[4,24,25,134,141,142] Therefore, for each separate analysis, the source population was included only once, resulting in 136 separate studies and 627 cases.

Definition of Poland syndrome

From the 121 studies stating a clear definition of Poland syndrome, we were able to distinguish 10 different definitions (Table 1).* Only 27 studies (20%) presented the classical definition of Poland syndrome.†

Patient characteristics

Out of 627 cases diagnosed with Poland syndrome, data about sex and affected side were available for 618 and 602 patients,‡ respectively. Sixty-five percent (n = 403) of the patients were male. The right side was affected in 58% of the cases (n = 352), the left side in

*3—5,10—19,22—25,27—30,32—35,37—49,51—63,65,66,68—73,75—78,80—95,97—100,102,105—107,109,110,112—116,118—135,137—143,145,146.

†3,15—17,27,34,52—54,56,57,59,68,73,77,83,87,89,91,93,97,114,115,123,129,130,140.

‡3—5,10—23,26—133,135—141,143—146.

TABLE 3. Observed Upper Extremity Deformities in the Presented Cases Derived From the Included Articles

Description of upper extremity deformity	n	Percentage
Any upper extremity deformity*	343	58
Ipsilateral symbrachydactyly (classic Poland syndrome)	178	29
Ipsilateral brachydactyly	56	9
Ipsilateral hypoplastic hand	56	9
Ipsilateral hand deformity (not further specified)	28	5
Ipsilateral forearm, ulnar, and radial hypoplasia/dysplasia	27	5
Ipsilateral thumb hypoplasia/dysplasia	27	5
Hypoplastic upper extremity	23	4
Ipsilateral adactyly 1–4 fingers	21	3
Ipsilateral syndactyly	14	2
Ipsilateral radioulnar synostosis	8	1
Ipsilateral transverse deficiency or absent hand	7	1
Ipsilateral clinodactyly	3	1
Ipsilateral camptodactyly	2	0.3
Ipsilateral complete adactyly	5	1
Contralateral hand or arm deformity	2	0.3
Others	9	2
Total number of clinically investigated upper extremity malformations	**588**	**100**

*Patients can have multiple upper extremity deformities.

39% (n = 237), and 2% (n = 13) had bilateral deficiencies. Genetic analysis was reported in 24 studies concerning 44 patients.[§] In 9 of these patients, copy number variations were observed,[20,21,25,36,135] such as duplications or deletions of a small region of a chromosome.

Chest and upper extremity deformities in Poland syndrome

Data on chest deformities at the patient level were included for 582 cases (Table 2).[‖] Hypoplasia or agenesis of the pectoralis major muscle, with or without involvement of the minor pectoral muscle, was described in 577 cases (99%).

Data on hand anomalies at the patient level were included for 588 cases. In 343 cases (58%), an upper extremity deformity was observed (Table 3).[¶] In only 178 cases (29%) did the authors describe a patient with symbrachydactyly, the classic Poland phenotype.[#] In the large cohort studies, Yiyit et al[4] and Catena et al[5] reported an incidence of symbrachydactyly of 9% and 40%, respectively, in patients diagnosed with Poland syndrome.

Associated abnormalities

In 277 cases, the presence of potentially associated abnormalities was clinically investigated and described in the articles. One or more associated abnormalities were found in 112 cases (cardiovascular, 10%; craniofacial, 9%; neurological, 8%; Sprengel deformity, 7%; oncological, 6%; urogenital, 4%; respiratory, 4%; dermatological, 4%); gastrointestinal, 4%; vertebral, 3%; hematological, 4%; leukemia, 3%; lower extremity, 1%; and other abnormalities, 3%).[**]

Familial cases

Eleven studies included in our systematic review describe a suggested familial occurrence of Poland syndrome (Table 4).[††] Maternally inherited copy number variants were identified in 4 patients in the study of Baban et al.[25] In contrast to the familiar occurrence of Poland

[§] 3,10,13,18,20–22,24,25,27,36,48,55,57,73,86,97,103,115,116,121,123,129,135.

[‖] 3,4,10–13,15–55,57–130,132,133,135–141,143,144,146.

[¶] 3–5,10–23,26–133,135–141,143–146.

[#] 3,10,13,15–19,21,22,27,28,32,33,36,37,39,42,44,48,50,51,53,54,57–59,63–67, 69–73,75,77,79,80,83–86,89–93,96,98,99,101,103–105,107–114,122–126,128–133, 138,139,141,144,146.

[**] 3,4,10,11,13,16–23,27–30,32,33,35–39,41,43–45,47–51,53,55,57–61,63–69,71, 73–78,80–82,85–92,94–101,103,105–107,109,110,113–122,125–127,130,132,133, 135–139,141,143,144.

[††] 4,25,26,35,41,86,114,123,126,129,137.

TABLE 4. Familial Poland Cases

Study	Sex	Familial Relation	Classic Poland Anomaly	Thoracic Deformities	Upper Limb Deformity	Other Abnormalities
Becker et al[26]	M		No	Absent head of the sternal head of the major pectoral muscle and a hypoplastic areola	-	-
	F	Cousin	No	Absent head of the sternal head of the major pectoral muscle, breast hypoplasia, and a hypoplastic areola	-	-
	M	Cousin	No	Absent head of the sternal head of the major pectoral muscle and a hypoplastic areola	-	-
Cohen et al[35]	M	-	No	Absent right major pectoral muscle	-	-
	F	Sibling	No	Absent right major pectoral muscle	-	-
Darian et al[41]	F	-	No	Absent major pectoral muscle aplasia of the breast and areolar deformities	-	Ulcerative colitis
	F	Cousin	No	Absent major pectoral muscle, underdeveloped chest wall, and hypoplasia of the breast	-	Ulcerative colitis
	F	Cousin	No	Absent major pectoral muscle, underdeveloped chest wall, and hypoplasia of the breast	-	-
	M	Cousin	No	Absent major pectoral muscle	-	Thoracic teratoma
	M	Cousin	No	Hypoplastic major pectoral muscle	-	-
David et al[42]	M	-	Yes	Absent left sternal head of major pectoral muscle	Ipsilateral brachydactyly and cutaneous syndactyly	-
	M	Grandfather	Yes	Absent left sternal head of major pectoral muscle	Ipsilateral brachydactyly and cutaneous syndactyly	
	M	Cousin	Yes	Absent left sternal head of major pectoral muscle	Ipsilateral brachydactyly and cutaneous syndactyly	
Larrandaburu et al[86]	F	-	Yes	Absent right sternal head of major pectoral muscle and hypoplasia of the breast	Ipsilateral symbrachydactyly	Psychomotor retardation, bilateral facial palsy, bilateral convergent strabismus, Möbius syndrome
	F	Aunt	No	Hypoplasia of right major pectoral muscle and breast	Ipsilateral brachydactyly	Mitral valve prolapse

(Continued)

TABLE 4. Familial Poland Cases (Continued)

Study	Sex	Familial Relation	Classic Poland Anomaly	Thoracic Deformities	Upper Limb Deformity	Other Abnormalities
	F	Cousin	No	-	Triphalangeal thumb	
	F	Cousin	No	-	Triphalangeal thumb	
	M	Cousin	No	-		Cleft palate
	M	Cousin	No	-		Club foot
Rojas-Martínez et al[114]	F	-	No	Hypoplastic major pectoral muscle, breast, and areola	Absent hand	Bilateral pes planus
	F	Mother	Yes	Hypoplastic major pectoral muscle, breast, and areola	Ipsilateral symbrachydactyly	-
Shalev et al[123]	M	-	No	Hypoplastic right chest	-	-
	F	Mother	No	Hypoplastic right breast, asymmetrical areola, fibrocystic changes in left breast	-	-
Soltan & Holmes[126]	F	-	No	Absent sternal head of the major pectoral muscle, amastia, and absent areola	-	-
	M	Sibling	No	-	-	Omphalocele
	F	Cousin	No	-	Transverse hemimelia	-
	M	Cousin	No	-	-	Unilateral microtia
	M	Uncle	No	-	Transverse hemimelia	-
Velez et al[137]	M	-	No	Major pectoral muscle hypoplasia	-	X-linked ichthyosis
	M	Sibling	No	Major pectoral muscle hypoplasia	Simple syndactyly	X-linked ichthyosis
Yiyit et al[4]	Reported a familiar occurrence in 4.4% of the cases (n = 113).					
Baban et al[25]	Reported 9 cases (4.2%) had at least 1 relative with a pectoral deformity; 16 cases (8.4%) had at least 1 relative with a thoracic or upper limb deformity, but with a normal pectoral muscle					

syndrome, Stevens et al[129] describe identical twin sisters without familiar occurrence; 1 of the sisters had a classic Poland anomaly, the other was unaffected.

Alternative diagnosis

Four different syndromes can present with hand, pectoral, and associated anomalies, namely: Holt-Oram syndrome, Duane radial ray syndrome, frontonasal dysplasia, and IVIC (Instituto Venezolano de Investigaciones Cientificas) syndrome.[6,7,147,148] Thirty-eight out of 67 eligible cases had at least 1 feature that matched 1 of the alternative syndromes.[‡‡] The alternative diagnosis that matched the presented phenotype most often was Duane radial ray syndrome (n = 32).[§§] The most frequently observed phenotypes that matched 1 of the syndromes are presented in Table 5.

DISCUSSION

In this systematic review, we studied the phenotypic spectrum of Poland syndrome in the literature. We reviewed 136 articles representing 627 patients, and we compared the applied definitions of Poland syndrome; observed hand, pectoral, and additional anomalies; and familial occurrence. Doing so, we illustrated the broad range of anomalies that were described using the eponym "Poland syndrome." By reviewing atypical cases with multiple congenital anomalies and cross-referencing these cases to

[‡‡]3,13,17,19,20,32,33,36,44,50,57,63,65,66,69,73,75,77,80,81,86,92,101,103,107,110,113,114,125,126,130,132,133,135,138,141.

[§§]3,17,19,20,32,33,36,44,50,63,65,66,69,73,75,77,80,81,86,92,101,103,110,113,114,126,130,133,135,141.

TABLE 5. Observed Phenotypes that Could Fit With One of the Alternative Syndromes*

Hand Anomalies		Associated Anomalies	
	Other		Other
Deficiencies of radioulnar axis development		Craniofacial	
Radioulnar synostosis	A, B, D	Facial weakness	B
Radial polydactyly	A, B	Ear anomalies	B, C, D
Radial longitudinal deficiency	A, B, D	Hypertelorism	B, C
Radial deficiency of hand plate	A, B, D	Broad nasal root	C
Triphalangeal thumb	A, B, D	Epicanthal fold	B, C
Ulnar longitudinal deficiency	B	Bifid nose tip	C
Muscle hypoplasia, other than pectoral muscle	B, D	Eye	
		Strabismus	B, D
		Optic disc anomalies (including coloboma)	B, C
		Skeletal	
		Khyphosis/scoliosis	A, B, D
		Vertebral anomalies	A, B
		Internal organs	
		Renal hypoplasia/agenesis	B
		Atrial septal defect	A, B
		Gastrointestinal anomalies (including pyloric stenosis)	B

*Alternative diagnoses: A, Holt-Oram syndrome; B, Duane radial ray syndrome; C, Frontonasal dysplasia, type 1; D, IVIC syndrome.

syndrome databases (HPO,[8] OMIM[9]), we were able to identify that 38 out of 67 atypical cases could fit an alternative diagnosis. Hence, we conclude that the use of the diagnosis Poland syndrome is widely variable in the current literature, which can lead to misclassification of a group of patients with pectoral muscle deficiencies. Therefore, we provide a list of phenotypes that might direct to an alternative diagnosis.

The data of the 136 included studies are largely in concordance with the data presented in the 3 largest studies included in this review.[4,5,140] Patient characteristics such as sex and the distribution of affected sides were comparable with those presented by Yiyit et al[4] and Catena et al.[5] Furthermore, both Yiyit et al[4] and Catena et al[5] present a minority of classic Poland syndrome cases (9% and 40%, respectively) in their samples. In our systematic review, 29% of the cases presented the phenotype described by Alfred Poland.[1] The true proportion of classic cases might be underestimated by both the work presented by Yiyit et al[4] and our review. Yiyit et al[4,141,142] published multiple articles on atypical Poland syndrome cases and even hypothesized that those cases represent a different syndrome. Therefore, the number of classic Poland syndrome cases they present might be an underestimation because a second syndrome could be highly prevalent in their study sample. Subsequently, our review could present a biased estimation because publication bias might contribute to a higher prevalence of atypical Poland cases in the literature.

Poland syndrome can be considered atypical based on phenotypical presentation as well as familial occurrence. Yiyit et al[4] described 5 patients with a family history of Poland syndrome and Baban et al[25] described that, in 24 of the cases, at least 1 of the features of Poland syndrome was prevalent in the family.[24] Unfortunately, not all studies that describe familial Poland cases were available under our library license. Darian et al[41] summarized several of these nonincluded studies and showed that 12 studies reported familial Poland cases in which pectoral muscle deficiencies and upper limb anomalies were present.

Strikingly, we observed that only 20% of the articles, which referred to the original description by Alfred Poland, used the original phenotype.[||||] Furthermore, 71% of the patients did not present a hand anomaly that matches the original description of Poland syndrome. Although most of these atypical hand anomalies

[||||] 3,14,16,17,27,34,52–54,56,57,59,68,73,77,83,87,88,91,93,97,114,115,123,129,130,140.

were etiologically alike, such as brachydactyly and syndactyly, hand anomalies of completely different etiology were also observed, such as cleft hand, radial dysplasia, triphalangeal thumbs, and thumb hypoplasia.[¶¶]

Using the correct description of Poland syndrome might seem a semantic dispute; however, the recognition of phenotypic deviation from an established syndrome is a key element in differential diagnosis. This is especially important in Poland syndrome, because the etiology of Poland syndrome is assumed to be multifactorial,[25,149] whereas multiple phenotypically similar syndromes have a genetic cause. Although some of these phenotypically similar syndromes have a genetic cause, only 44 patients in our review underwent a genetic work-up.[##] Possibly, for many clinicians and patients, the diagnosis of Poland syndrome is sufficiently explanatory for the observed anomalies and, therefore, no genetic screening is performed. Therefore, an incorrect diagnosis might influence decision making in genetic research.

We identified 4 possible alterative diagnoses from the HPO dataset,[8] syndromes that can also present with pectoral anomalies. For the 67 cases with multiple congenital anomalies, 38 cases presented with at least 1 of the features of an alternative diagnosis. The most frequently observed overlap was with Duane radial ray syndrome.[6] The defining phenotypic features of this syndrome are eye anomalies and radial (longitudinal) deficiencies of the upper limb. To illustrate this, the phenotypes presented by Bosch-Banyeras et al,[27] Parker et al,[101] and Mut et al[96] could be suggestive for Duane radial ray syndrome. Likewise, the combination of thumb hypoplasia and cardiac defects (atrial septal defect)[19] could be suggestive for Holt-Oram syndrome.[7] However, for both syndromes, incomplete penetrance has been described, meaning that patients can present without the associated anomalies. Considering the high prevalence of thumb hypoplasia, the true proportion of patients with Duane radial ray or Holt-Oram syndrome in our population could easily exceed our estimation. For these unrecognized patients, this might imply that "hidden" associated anomalies might not be detected due to the lack of diagnostic tests, such as an echocardiogram. In addition, the recurrence risk for the next generation might be underestimated. However, most importantly, this review describes only those anomalies and syndromes related to pectoral muscle deficiency that were identifiable using a selected search. It is possible that pectoral muscle deficiency also sporadically co-occurs with other syndromes. Especially in the cases with radial deficiencies, we should always rule out more severe syndromes, such as Fanconi anemia. Although the odds of misdiagnosing a case with Fanconi syndrome as Poland syndrome might be low, the consequences, when the indicated work-up and treatment is not applied, are life threatening.

The phenotypic features of the alternative diagnoses we encountered in our study population can be used as a guideline for clinicians encountering atypical Poland syndrome. However, the content of Table 5 is not the complete phenotypic spectrum of these syndromes, but rather an indication of what kind of anomalies could be present. Multiple hand anomalies can be observed with the alternative syndromes. Malformations affecting the radioulnar axis of development[150] are suspicious for Holt-Oram syndrome, IVIC syndrome, and Duane radial ray syndrome.[6,7,148] We also encountered patients with cleft hand and feet.[63,140] Although, strictly speaking, there are no relations to pectoralis major deficiencies, there are syndromes that can present with cleft hands and breast aplasia (ectrodactyly-ectodermal dysplasia or adult syndrome[151,152]). In general, we therefore consider that any hand anomaly besides symbrachydactyly should indicate to the clinician the need for a thorough physical examination to detect possible associated anomalies.

In conclusion, there is enough evidence to support our statement that the term "Poland syndrome" should not be used as a synonym for what, in fact, is pectoral hypoplasia or pectoral deficiency. Pectoral muscle hypoplasia is not distinctive for Poland syndrome alone, but is also present in syndromes with other associated anomalies with an entirely different pattern of inheritance. To prevent diagnostic and prognostic errors in patients with an atypical phenotype, we recommend that other syndromes be ruled out before diagnosing a patient with Poland syndrome. As a result, increased attention for patients with Poland-like phenotypes might lead to new evidence concerning the etiology of Poland syndrome or the identification of potential subsyndromes.

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[¶¶] 5,19,33,57,63,70,75,83,86,101,105,140.

[##] 3,10,13,18,20–22,24,25,27,36,48,55,57,73,86,97,103,115,116,121,123,129,135.

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APPENDIX B. Search Strategy

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('Poland syndrome'/exp OR ('pectoralis major muscle'/exp AND 'hand malformation'/exp) OR ((Poland* NEAR/6 (syndrome* OR syndactyl* OR brachysyndactyl* OR anomal* OR complex* OR symbrachydact* OR sequence* OR deformit* OR ectrosyndact*)) OR ((pectoral* NEAR/3 (muscl* OR dysplas* OR agenes* OR absen*)) AND ((hand NEAR/3 (deformit* OR malformat* OR anomal*)) OR syndact* OR brachysyndactyl*))):ab,ti) AND (phenotype/de OR 'phenotypic variation'/exp OR 'phenotypic plasticity'/exp OR etiology/exp OR pathophysiology/exp OR development/exp OR genetics/exp OR heredity/exp OR 'vascular disease'/exp OR 'blood vessel'/exp OR pathology/exp OR 'familial disease'/exp OR 'disease classification'/exp OR 'disease association'/exp OR (phenotyp* OR pathogen* OR patholog* OR etiopathogen* OR aetiopathogen* OR etiolog* OR aetiolog* OR pathophysiolog* OR characteri* OR heterogen* OR homogen* OR develop* OR genetic* OR inherit* OR heredit* OR famil* OR vascul* OR vessel* OR arter* OR thrombo* OR associat* OR variant* OR variation* OR form OR forms OR bilateral* OR present* OR polymorph* OR caus*):ab,ti)

Medline (OvidSP)

(Poland syndrome/ OR (Pectoralis Muscles/ AND exp Hand Deformities/) OR ((Poland* ADJ6 (syndrome* OR syndactyl* OR brachysyndactyl* OR anomal* OR complex* OR symbrachydact* OR sequence* OR deformit* OR ectrosyndact*)) OR ((pectoral* ADJ3 (muscl* OR dysplas* OR agenes* OR absen*)) AND ((hand ADJ3 (deformit* OR malformat* OR anomal*)) OR syndact* OR brachysyndactyl*))).ab,ti.) AND (exp phenotype/ OR etiology.xs. OR exp causality/ OR pathophysiology.xs. OR exp Growth and Development/ OR "Growth and Development".xs. OR genetics.xs. OR exp genetics/ OR exp heredity/ OR exp vascular diseases/ OR exp blood vessels/ OR pathology.xs. OR exp pathology/ OR exp classification/ OR classification.xs. OR (phenotyp* OR pathogen* OR patholog* OR etiopathogen* OR aetiopathogen* OR etiolog* OR aetiolog* OR pathophysiolog* OR characteri* OR heterogen* OR homogen* OR develop* OR genetic* OR inherit* OR heredit* OR famil* OR vascul* OR vessel* OR arter* OR thrombo* OR associat* OR variant* OR variation* OR form OR forms OR bilateral* OR present* OR polymorph* OR caus*).ab,ti.)

Cochrane

(((Poland* NEAR/6 (syndrome* OR syndactyl* OR brachysyndactyl* OR anomal* OR complex* OR symbrachydact* OR sequence* OR deformit* OR ectrosyndact*)) OR ((pectoral* NEAR/3 (muscl* OR dysplas* OR agenes* OR absen*)) AND ((hand NEAR/3 (deformit* OR malformat* OR anomal*)) OR syndact* OR brachysyndactyl*))):ab,ti) AND ((phenotyp* OR pathogen* OR patholog* OR etiopathogen* OR aetiopathogen* OR etiolog* OR aetiolog* OR pathophysiolog* OR characteri* OR heterogen* OR homogen* OR develop* OR genetic* OR inherit* OR heredit* OR famil* OR vascul* OR vessel* OR arter* OR thrombo* OR associat* OR variant* OR variation* OR form OR forms OR bilateral* OR present* OR polymorph* OR caus*):ab,ti)

Web of Science

TS=((((Poland* NEAR/6 (syndrome* OR syndactyl* OR brachysyndactyl* OR anomal* OR complex* OR symbrachydact* OR sequence* OR deformit* OR ectrosyndact*)) OR ((pectoral* NEAR/3 (muscl* OR dysplas* OR agenes* OR absen*)) AND ((hand NEAR/3 (deformit* OR malformat* OR anomal*)) OR syndact* OR brachysyndactyl*)))) AND ((phenotyp* OR pathogen* OR patholog* OR etiopathogen* OR aetiopathogen* OR etiolog* OR aetiolog* OR pathophysiolog* OR characteri* OR heterogen* OR homogen* OR develop* OR genetic* OR inherit* OR heredit* OR famil* OR vascul* OR vessel* OR arter* OR thrombo* OR associat* OR variant* OR variation* OR form OR forms OR bilateral* OR present* OR polymorph* OR caus*)))

PubMed Publisher

(Poland syndrome[mh] OR (Pectoralis Muscles [mh] AND Hand Deformities[mh]) OR ((Poland* [tiab] AND (syndrome*[tiab] OR syndactyl*[tiab] OR brachysyndactyl*[tiab] OR anomal*[tiab] OR complex*[tiab] OR symbrachydact*[tiab] OR sequence*[tiab] OR deformit*[tiab] OR ectrosyndact*[tiab])) OR ((pectoral*[tiab] AND (muscl* [tiab] OR dysplas*[tiab] OR agenes*[tiab] OR absen*[tiab])) AND ((hand AND (deformit*[tiab] OR malformat*[tiab] OR anomal*[tiab])) OR syndact*[tiab] OR brachysyndactyl*[tiab])))) AND (phenotype[mh] OR etiology[sh] OR causality[mh] OR pathophysiology[sh] OR Growth and Development[mh] OR "Growth and Development"[sh] OR genetics[sh] OR genetics[mh] OR heredity[mh] OR vascular diseases[mh] OR blood vessels[mh] OR pathology[sh] OR pathology[mh] OR classification

[mh] OR classification[sh] OR (phenotyp*[tiab] OR pathogen*[tiab] OR patholog*[tiab] OR etiopathogen*[tiab] OR aetiopathogen*[tiab] OR etiolog*[tiab] OR aetiolog*[tiab] OR pathophysiolog*[tiab] OR characteri*[tiab] OR heterogen*[tiab] OR homogen*[tiab] OR develop*[tiab] OR genetic*[tiab] OR inherit*[tiab] OR heredit*[tiab] OR famil*[tiab] OR vascul*[tiab] OR vessel*[tiab] OR arter*[tiab] OR thrombo*[tiab] OR associat*[tiab] OR variant*[tiab] OR variation*[tiab] OR form OR forms OR bilateral*[tiab] OR present*[tiab] OR polymorph*[tiab] OR caus*[tiab])) AND publisher[sb]

Google Scholar

"Poland|Polands syndrome|anomaly|complex|sequence|deformity" phenotype|pathogenesis|pathology|etiopathogenesis|etiology|aetiology|pathophysiology|characterization|development|genetic|genetics|vascular|vessel|thrombosis|variant|variation|forms|causality

Human Phenotype Ontology Database

File name: ALL_SOURCES_ALL_FREQUENCIES_diseases_to_genes_to_phenotypes.txt

Accession date: February 22th of 2017

Used phenotypic terms for pectoral muscle deficiency:

Pectoral muscle hypoplasia/aplasia HP:0005258

Pectoralis major hypoplasia HP:0008953

Pectoralis hypoplasia HP:0008998

Aplasia of the pectoralis major muscle HP:0009751