

REVIEW

Maternal known drug allergy and long-term dermatological morbidity of the offspring

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Abstract

Drug allergy is associated with adverse short-term perinatal outcomes such as caesarian delivery and preterm delivery. The aim of the present study was to determine whether being born to a mother with known drug allergy increases the risk for long-term dermatological morbidity of the offspring. A population-based cohort study, comparing long-term dermatological morbidity of offspring to mothers with and without known drug allergy, was conducted. Dermatological morbidity was assessed up to the age of 18 years according to a predefined set of ICD-9 codes associated with hospitalization of the offspring. A Kaplan-Meier survival curve was used to compare cumulative incidence of long-term dermatological morbidity, and a Cox proportional hazards model was constructed to control of confounders. During the study period, 243,682 deliveries met the inclusion criteria, of them 4% (n = 9756) were of mothers with known drug allergy. Offspring born to mothers with known drug allergy had higher rates of long-term dermatological morbidity. Likewise, the cumulative incidence of long-term dermatological morbidity was higher as compared with those without known drug allergy (Kaplan-Meier log-rank $P = .021$). Using a Cox proportional hazards model, controlling for confounders, being born to a mother with known drug allergy was found to be an independent risk factor for long-term dermatological morbidity of the offspring (adjusted HR 1.2, 95% CI 1.03-1.33, $P = .016$). Being born to a mother with known drug allergy is independently associated with higher risk for long-term dermatological morbidity of the offspring.

KEYWORDS

dermatological morbidities, drug allergy, offspring, pregnancy outcomes

Abbreviations: DHR, Drug hypersensitivity reaction; DIHS, drug-induced hypersensitivity syndrome; GDM, gestational diabetes mellitus; ICD-9, International Classification of Disease; IUGR, intrauterine growth restriction; SUMC, Soroka University Medical Center.

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1 | INTRODUCTION

Drug allergy is a common problem list item with prevalence that ranges between 7% to 8% among the general population.^{1,2} Drug hypersensitivity reaction (DHR) is defined as an unpredictable, idiosyncratic immune reaction to drug therapy.³ While it has the potential to cause life-threatening reactions such as anaphylaxis,⁴ the most common allergic manifestations of DHR are skin reactions, such as urticaria, angioedema, or drug-induced hypersensitivity syndrome (DIHS).^{5,6}

Successful coexistence between the mother and the semi-allograft fetus is possible due to maternal immunological adaptations that occur during pregnancy.⁷ Immunosuppressive factors produced by the placenta cause an elevation of regulatory T cells (TReg) and a suppression of cytotoxic attack by NK and T cells, resulting in maternal immune system suppression response.^{8,9} Inadequate immune adaptation can lead to hostile intrauterine environment and adverse pregnancy outcomes.^{10,11}

Pregnancy complications such as hypertensive disorders and gestational diabetes mellitus (GDM) have been shown to be associated with a history of maternal drug allergy. Moreover, need for fertility treatment, preterm delivery, and intrauterine growth restriction (IUGR) were all found to be higher among women with known drug allergy.¹²

The prevalence of childhood atopic dermatitis, psoriasis, allergic immune skin reactions, and other allergic diseases has been shown to steadily increase in recent years.¹³ While studies demonstrated genetic components of different childhood allergic phenotypes that appear strongly heritable, these inherited components do not follow the simple mendelian pattern, and the specific genes responsible for these inherited components have not been determined.¹⁴ Other studies have associated common childhood allergic diseases such as asthma, atopic dermatitis, and eczema with pre- and perinatal factors such as maternal age,¹⁵ maternal diet during pregnancy,¹⁶ fertility treatments,¹⁷ prenatal medication exposure,¹⁸ and adverse pregnancy outcomes such as preeclampsia and preterm delivery.¹⁹ A possible biological mechanism for an association between maternal drug allergy and long-term dermatological morbidity of the offspring can be derived from an altered maternal immune response that may influence the normal development of the fetal immune system and may result in long-term dermatological morbidity. Several mechanisms such as cord blood levels of immunological factors,²⁰ Th2 cell-related chemokines,²¹ and allergens²² and antibodies²³ that cross the placenta may play a major role in this association.

The aim of the present study was to determine whether being born to a mother with known drug allergy increases the risk for long-term dermatological morbidity of the offspring.

2 | MATERIALS AND METHODS

2.1 | Setting

The study was conducted at Soroka University Medical Center (SUMC), a tertiary hospital serving the entire population of the

region with 15 000 to 17 000 deliveries annually. The study was approved by the institutional review board in accordance with Helsinki Declaration (IRB number 0357-19-SOR).

2.2 | Study population

All singleton deliveries between 1991-2014 at SUMC were included in the study. Offspring with congenital malformations were excluded from the study. Cases of perinatal death were excluded from the long-term analysis.

2.3 | Study design

A population-based cohort study, comparing long-term dermatological morbidity of offspring to mothers with and without known drug allergy, was conducted. The primary exposure was defined as known maternal drug allergy. The main outcome was defined as offspring's long-term dermatological morbidity up to 18 years. Dermatological morbidity was assessed according to a predefined set of ICD-9 codes associated with hospitalization of the offspring. Dermatological morbidity included dermatitis, psoriasis, allergic, and immune skin reactions (Appendix 1). Hospitalization due to any medical condition with dermatological conditions as a primary or secondary diagnosis was considered as an event, even when other medical conditions were the main cause for the hospitalization. Only the first hospitalization for each child was included in the analysis. Follow-up was terminated either when at first hospitalization with dermatological diagnosis occurred, the child reached 18 years of age, or when the child died for non-dermatological reasons.

2.4 | Data collection method

Data were collected from two databases that were cross-linked and merged: the computerized perinatal database of the Obstetrics and Gynecology department and the pediatric hospitalization database ("Demog-ICD9"). The obstetrical database includes demographic information, perinatal assessments, maternal morbidities, and maternal and fetal outcomes, recorded by the attending physician immediately following delivery. Records were anonymized prior to analysis. The pediatric hospitalization database includes demographic information and international classification of diseases, ninth revision codes (ICD-9), for all medical diagnosis made during any hospitalization. All newborns in the country are issued with a national security number (ID number) which is then registered in the mother's formal identification card. These identification numbers are not changed nor duplicated within the population at any given time. This allows certainty of the relationship between any mother and child in our datasets.

2.5 | Statistical analysis

Univariable analysis was performed to compare background characteristics between the two study groups. The univariable analysis included chi-square tests for categorical variables, and *t* tests or Man-Whitney *U* tests for continuous variables, according to their distribution. Cumulative incidence rates were compared using Kaplan-Meier, using the log-rank test to determine significant differences. Cox proportional hazards model was conducted to compare dermatologic-associated hospitalizations risk among offspring born to mothers with and without known drug allergy, adjusting to length of follow-up. The model was adjusted for potential confounders based on the univariable analysis, and on clinical importance of the variables. The mothers in the cohort were entered as clusters to account for dependence between siblings. The final model was chosen based on best fit and minimal $-2\log$ likelihood. All analyses were performed using SPSS package 23rd. ed. as well as the STATA software 12th edition.

3 | RESULTS

During the study period 243,682 deliveries were included, of which 4% (*n* = 9756) were of mothers with known drug allergy. Table 1 presents demographic characteristics and perinatal outcomes of the study population. Women with known drug allergy were older, with lower parity order, and were more likely to conceive following fertility treatments, as compared to women without known drug

allergy. Hypertensive disorders, maternal diabetes, and caesarian delivery were higher among women with known drug allergy as compared to the comparison group (7.2% vs 4.9%, 8.2% vs 4.9%, and 21.1% vs 13.2% for hypertensive disorders, maternal diabetes, and caesarian delivery, respectively; *P* < .001). Higher rates of preterm delivery were also noted among mothers with known drug allergy (7.7% vs 6.8%, *P* < .001). Women with known maternal drug allergy had lower rates of ante-partum death compared to women without known drug allergy (with a protective OR, 0.2% vs 0.3%, *P* = .009). Nevertheless, no differences were noted between the groups regarding intrapartum death and post-partum death (*P* = .755 and 0.513, respectively).

Table 2 describes the association between maternal known drug allergy and long-term dermatological morbidity of the offspring. After excluding all cases of perinatal mortality (*n* = 1340), total dermatological hospitalization rate was higher among offspring to mothers with known drug allergy as compared to the controls (2.6% vs 2.2%, *P* = .01). Specifically, allergic reactions and autoimmune diseases were significantly higher among offspring of mothers with known drug allergy. Likewise, a Kaplan-Meier survival curve demonstrated higher cumulative incidence of dermatological morbidity in children born to mother with known drug allergy as compared to the unexposed offspring (log-rank, *P* = .021, Figure 1). In the Cox proportional hazards model which controlled for maternal age, hypertensive disorders, gestational age, caesarian delivery, and maternal diabetes mellitus, being born to a mother with known drug allergy was found to be an independent risk factor for long-term dermatological morbidity of the offspring (adjusted HR 1.2, 95% CI 1.03-1.33; *P* = .016, Table 3).

TABLE 1 Population characteristics by study groups

Characteristics	Women with drug allergy (<i>n</i> = 9756) %	No drug allergy (<i>n</i> = 233 926) %	OR	95% CI	<i>P</i> value
Maternal age, y (mean ± SD)	30.28 ± 5.3	28.07 ± 5.8			<.001
Parity					
1	27.5	23.4			
2-4	60.4	50.7			
5+	12.1	25.8			<.001
Maternal hypertensive disorders*	7.2	4.9	1.5	1.38-1.62	<.001
Maternal diabetes mellitus**	8.2	4.9	1.7	1.62-1.88	<.001
Mode of delivery					
Assisted vaginal delivery	2.6	3.2			
Caesarian delivery	21.1	13.2			<.001
Preterm delivery	7.7	6.8	1.1	1.06-1.23	.001
Perinatal mortality					
Ante-partum death	0.2	0.3	0.5	0.3-0.85	.009
Intrapartum fetal death	0.01	0.01	0.7	0.19-3.27	.755
Post-partum death	0.2	0.2	1.14	0.76-1.72	.43

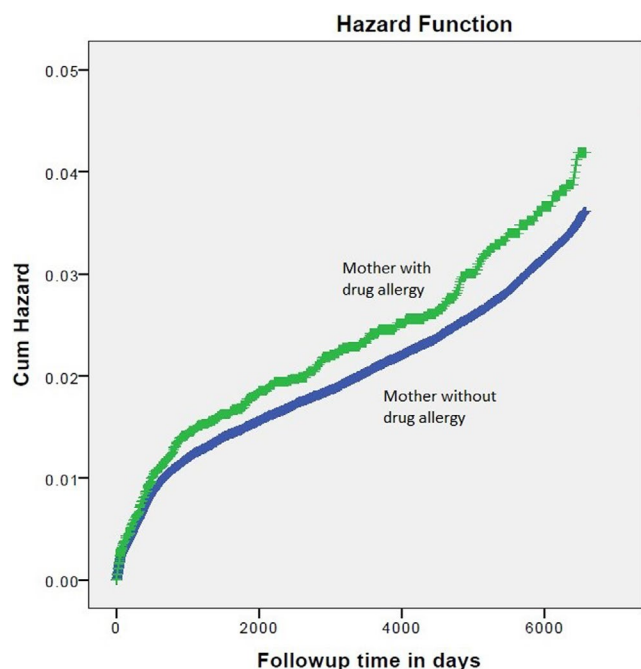
Abbreviations: CI, confidence interval; IVF, invitro fertilization; OI, ovulation induction; OR, odds ratio.

*Hypertensive disorders include chronic hypertension, gestational hypertension and preeclampsia.

**Maternal diabetes mellitus includes pre-gestational and gestational diabetes mellitus.

TABLE 2 The association between maternal known drug allergy and long-term dermatological morbidity of the offspring

Offspring long-term dermatological morbidity	Maternal drug allergy (n = 9714) %	No drug allergy (n = 232,628) %	OR	95% CI	P value
Dermatitis, psoriasis	0.5	0.4	1.2	0.9-1.6	.209
Allergic reaction, immune disease	0.3	0.2	1.76	1.2-2.6	.004
Other	1.3	0.9	1.43	1.2-1.71	<.001
Total dermatologic hospitalization	2.6	2.2	1.18	1.04-1.34	.01

**FIGURE 1** A Kaplan-Meier survival curve demonstrating the cumulative incidence of long-term dermatological morbidity of the offspring according to maternal drug allergy. (log-rank, $P = .021$)

4 | DISCUSSION

In this large population-based study, maternal known drug allergy was an independent risk factor for long-term dermatological morbidity of the offspring. Furthermore, pregnancies of mothers with known drug allergy have been found to be associated with adverse pregnancy outcomes such as hypertensive disorders, maternal diabetes, caesarian delivery, and preterm delivery.

During pregnancy, the maturation of the embryonal immune system can be altered by different maternal conditions and exposures, which results in allergic or other immunological diseases later in life. Together with our study findings, maternal inflammation,²⁴ maternal microbiome,²⁵ parental history of atopic disease,²⁶ and maternal diet during pregnancy²⁷ have all been associated with childhood allergic dermatological conditions such as eczema and atopic dermatitis. As drug allergy has been shown to be associated with immunological intolerance, maternal known drug allergy may affect the developing fetal immune system, resulting in dermatological and allergic morbidity later during childhood.

It was already shown that maternal IgG and allergens can cross through the placenta, influencing the child's immune system.^{22,23}

Yet, the linkage between cord blood levels of maternal immunoglobulins to child's atopy and allergy remains unclear.^{28,29}

During normal pregnancy, the placenta produces placental growth hormone, which plays a significant role in maternal-fetal immunotolerance system.^{9,30} Women with drug allergies have been shown to have inadequate immunotolerance mechanism, with altered cytokine responses to allergens compared to non-allergic women.^{31,32} Moreover, an altered immune response during pregnancy may cause abnormal inflammatory reaction,³³ and high levels of cord blood Th2 cell-related chemokines have been shown to be linked with allergy²¹ and atopic dermatitis²⁰ of the offspring. The inadequate maturing of the child immunologic system may be the reason for autoimmune mechanism of dermatological diseases in later life.

Maternal known drug allergy may not exclusively affect the child's risk for dermatological morbidities via in-utero exposure. Low levels of CD14 cells in the maternal colostrum were associated with higher risk for atopic dermatitis among children born to mothers with allergies.³⁴

From a genetic perspective, drug allergy induced by IgE and delayed T-cell mechanisms appear to be related to several human leukocyte antigen (HLA) variants and specific gene expression.³⁵ There is an association between some dermatological diseases and these group of HLA variants such as HLA-B*1502³⁶ and HLA-B*5801.³⁷ Although the inheritance pattern of these genetic factors is not fully understood, some dermatological diseases are linked with such genetic predisposition.³⁸⁻⁴⁰

The main strength of this study is derived from its large population. Being the sole hospital in the southern part of the country, SUMC allows us to maintain a steady follow-up after the offspring, for a long-term period.

Nevertheless, this study had some limitations. Our study has been done as a retrospective population-level analysis; hence, this study can provide evidence only of association and not causation. We did not include some demographic characteristics such as social status, economic status, and residential aspects of the mother and the offspring that may also contribute to dermatological morbidity, including information regarding tobacco consumption and maternal use of drugs during pregnancy. Finally, our study included only hospitalized children. It is expected that many dermatological conditions in children were managed in ambulatory setting, and only those complicated or severe diseases required hospitalization. Nevertheless, among those cases that were hospitalized, the association between maternal known drug allergy and the child's dermatological morbidity has been demonstrated.

In conclusion, our results show that alongside with several adverse pregnancy outcomes, maternal known drug allergy is an

TABLE 3 Cox proportional hazards model for long-term dermatological morbidity of the offspring

Outcome	Adjusted HR	95% CI	P value
Maternal drug allergy (vs no drug allergy)	1.2	1.03-1.33	.016
Gestational age (weeks)	0.9	0.95-0.97	<.001
Maternal age (years)	0.9	0.98-0.99	<.001
Hypertensive disorders	0.8	1.03-1.32	.280
Maternal diabetes mellitus	1.0	0.94-1.20	.278
Cesarean delivery	1.0	0.97-1.17	.174

independent risk factor also for long-term dermatological morbidities of the offspring.

Maternal drug allergy is a vital component of her history and as research advances, this information is expected to have a clinical impact on the management of her offspring; suspicion thresholds and diagnostic efforts would be properly set to address certain population subsets, and with timely diagnosis—the rate of hospitalizations may be minimized.

5 | CONCLUSION

Our population-based cohort study showed that known maternal drug allergy is an independent risk factor for dermatological morbidities in later life. Further investigations can narrow the investigated drug allergy spectrum to specific drug allergies and their effects on perinatal outcomes and long-term health of the offspring.

CONFLICT OF INTEREST

The authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

The data are not publicly available due to privacy or ethical restrictions (IRB committee restrictions)

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APPENDIX 1

Diagnosis Code	Diagnosis Desc
6800	CARBUNCLE AND FURUNCLE OF FACE
6801	CARBUNCLE AND FURUNCLE OF NECK
6805	CARBUNCLE AND FURUNCLE OF BUTTOCK
6806	CARBUNCLE AND FURUNCLE OF LEG, EXCEPT FOOT

Diagnosis Code	Diagnosis Desc
6809	CARBUNCLE AND FURUNCLE OF UNSPECIFIED SITE
68 100	UNSPECIFIED CELLULITIS AND ABSCESS OF FINGER
68 102	ONYCHIA AND PARONYCHIA OF FINGER
6811	CELLULITIS AND ABSCESS OF TOE
68 110	UNSPECIFIED CELLULITIS AND ABSCESS OF TOE
68 111	ONYCHIA AND PARONYCHIA OF TOE
6819	CELLULITIS AND ABSCESS OF UNSPECIFIED DIGIT
6820	CELLULITIS AND ABSCESS OF FACE
6821	CELLULITIS AND ABSCESS OF NECK
6822	CELLULITIS AND ABSCESS OF TRUNK
6823	CELLULITIS AND ABSCESS OF UPPER ARM AND FOREARM
6824	CELLULITIS AND ABSCESS OF HAND, EXCEPT FINGERS AND THUMB
6825	CELLULITIS AND ABSCESS OF BUTTOCK
6826	CELLULITIS AND ABSCESS OF LEG, EXCEPT FOOT
6827	CELLULITIS AND ABSCESS OF FOOT, EXCEPT TOES
6828	CELLULITIS AND ABSCESS OF OTHER SPECIFIED SITES
6828 1	ABSCESS OF SCALP
6829	CELLULITIS AND ABSCESS OF UNSPECIFIED SITES
683	ACUTE LYMPHADENITIS
684	IMPETIGO
6850	PILONIDAL CYST WITH ABSCESS
6851	PILONIDAL CYST WITHOUT MENTION OF ABSCESS
68 600	PYODERMA, UNSP.
68 609	OTHER PYODERMA
6861	PYOGENIC GRANULOMA OF SKIN AND SUBCUTANEOUS TISSUE
6868	SPECIFIED LOCAL INFECTIONS OF SKIN & SUBCUTANEOUS TISSUE
6869	UNSPECIFIED LOCAL INFECTION OF SKIN AND SUBCUTANEOUS TISSUE
690	ERYTHEMATOSQUAMOUS DERMATOSIS
6901	SEBORRHEIC DERMATITIS
69 010	SEBORRHEIC DERMATITIS, UNSPECIFIED
69 011	SEBORRHEA CAPITIS
69 012	SEBORRHEIC INFANTILE DERMATITIS
6910	DIAPER OR NAPKIN RASH
6918	OTHER ATOPIC DERMATITIS AND RELATED CONDITIONS
6924	CONTACT DERMATITIS + ECZEMA DUE TO OTHER CHEMICAL PRODUCTS
6925	CONTACT DERMATITIS + ECZEMA DUE TO FOOD IN CONTACT WITH SKIN

Diagnosis Code	Diagnosis Desc
69 271	SUNBURN
69 272	ACUTE DERMATITIS DUE TO SOLAR RADIATION
6929	CONTACT DERMATITIS AND OTHER ECZEMA, UNSPECIFIED CAUSE
6930	DERMATITIS DUE TO DRUGS AND MEDICINES TAKEN INTERNALLY
6931	DERMATITIS DUE TO FOOD TAKEN INTERNALLY
6940	DERMATITIS HERPETIFORMIS
6941	SUBCORNEAL PUSTULAR DERMATOSIS
6944	PEMPHIGUS
6945	PEMPHIGOID
6948	OTHER SPECIFIED BULLOUS DERMATOSES
6949	UNSPECIFIED BULLOUS DERMATOSES
6950	TOXIC ERYTHEMA
6951	ERYTHEMA MULTIFORME
69 510	ERYTHEMA MULTIFORME, UNSPECIFIED
69 512	ERYTHEMA MULTIFORME MAJOR
69 513	STEVENS-JOHNSON SYNDROME
69 515	TOXIC EPIDERMAL NECROLYSIS
6952	ERYTHEMA NODOSUM
6953	ROSACEA
6954	LUPUS ERYTHEMATOSUS
69 559	EXFOLIATION DUE TO ERYTHEMATOUS CONDITION INVOLVING 90 PERCENT OR MORE OF BODY SURFACE
69 581	RITTER'S DISEASE
69 589	OTHER SPECIFIED ERYTHEMATOUS CONDITIONS
6959	UNSPECIFIED ERYTHEMATOUS CONDITION
6961	OTHER PSORIASIS AND SIMILAR DISORDERS
6962	PARAPSORIASIS
6963	PITYRIASIS ROSEA
6965	OTHER AND UNSPECIFIED PITYRIASIS
6970	LICHEN PLANUS
6982	PRURIGO
6984	DERMATITIS FACTITIA (ARTEFACTA)
6989	UNSPECIFIED PRURITIC DISORDER
700	CORNS AND CALLOSITIES
7010	CIRCUMSCRIBED SCLERODERMA
7011	KERATODERMA, ACQUIRED
7012	ACQUIRED ACANTHOSIS NIGRICANS
7013	STRIAE ATROPHICAE
7014	KELOID SCAR
7018	OTHER SPECIFIED HYPERTROPHIC AND ATROPHIC CONDITIONS OF SKIN
7019	UNSPECIFIED HYPERTROPHIC AND ATROPHIC CONDITIONS OF SKIN
7020	ACTINIC KERATOSIS
70 219	OTHER SEBORRHEIC KERATOSIS

Diagnosis Code	Diagnosis Desc
7028	OTHER SPECIFIED DERMATOSES
7060	ACNE VARIOLIFORMIS
7063	SEBORRHEA
7070	DECUBITUS ULCER
70 700	PRESSURE ULCER, UNSPECIFIED SITE
70 701	PRESSURE ULCER, ELBOW
70 702	PRESSURE ULCER, UPPER BACK
70 703	DECUBITUS ULCER, LOWER BACK
70 703	PRESSURE ULCER, LOWER BACK
70 704	DECUBITUS ULCER, HIP
70 704	PRESSURE ULCER, HIP
70 705	PRESSURE ULCER, BUTTOCK
70 706	PRESSURE ULCER, ANKLE
70 707	DECUBITUS ULCER, HEEL
70 707	PRESSURE ULCER, HEEL
70 709	DECUBITUS ULCER OTHER SITE
70 709	PRESSURE ULCER OTHER SITE
70 710	UNSPECIFIED ULCER OF LOWER LIMB
70 711	ULCER OF THIGH
70 712	ULCER OF CALF
70 713	ULCER OF ANKLE
70 714	ULCER OF HEEL AND MIDFOOT
70 715	ULCER OF OTHER PART OF FOOT
70 719	ULCER OF OTHER PART OF LOWER LIMB
70 720	PRESSURE ULCER, UNSPECIFIED STAGE
70 721	PRESSURE ULCER STAGE I
70 722	PRESSURE ULCER STAGE II
70 723	PRESSURE ULCER STAGE III
70 724	PRESSURE ULCER STAGE IV
7078	CHRONIC ULCER OF OTHER SPECIFIED SITES
7079	CHRONIC ULCER OF UNSPECIFIED SITE
7080	ALLERGIC URTICARIA
7083	DERMATOGRAPHIC URTICARIA
7088	OTHER SPECIFIED URTICARIA
7089	UNSPECIFIED URTICARIA
7100	SYSTEMIC LUPUS ERYTHEMATOSUS
7101	SYSTEMIC SCLEROSIS
7102	SICCA SYNDROME
7103	DERMATOMYOSITIS
7104	POLYMYOSITIS
70 583	HIDRADENITIS
7068	OTHER SPECIFIED DISEASES OF SEBACEOUS GLANDS
7091	VASCULAR DISORDERS OF SKIN
7821	RASH AND OTHER NONSPECIFIC SKIN ERUPTION
7829	OTHER SYMPTOMS INVOLVING SKIN AND INTEGUMENTARY TISSUES