

Segmental Pigmentation Disorder: Clinical Manifestations and Epidemiological Features in 144 patients, a Retrospective Case-control Study

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Segmental pigmentation disorder (SPD) is characterized by hypo- or hyper-pigmented patches segmentally distributed, present in infancy, more prominently in darker-skinned children. The aim of this study was to define the demographic and clinical characteristics of SPD in a large series of patients. This was a retrospective case-control study at 2 paediatric dermatology centres in Israel. Data were collected through a telephone questionnaire and medical records. The study group consisted of 144 individuals with SPD and 144 individuals visiting the same institutions matched for age and sex. Median age of onset of SPD was near birth; 51% of patients were Sephardic Jews, and patients were followed up for a median period of 27 years. The patches were located on the torso (43%), mostly hypopigmented (52%), and remained of the same intensity and size in 55% and 41% of cases, accordingly. No differences in extracutaneous morbidities were found between SPD and control patients. This study delineates the demographic and clinical characteristics of SPD, confirms that cutaneous findings in SPD are more prominent in darker skin, tends not to expand in size or accentuate throughout the years, nor to be associated with extracutaneous morbidities.

Key words: pigmentation; segmental; mosaicism; extracutaneous manifestations.

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In 1983, the term segmental pigmentation disorder (SPD) was first introduced by Metzker (1), referring to a phenomenon prevalent among dark-skinned children, consisting of hypo- or hyper-pigmented patches and featuring a segmental distribution with a sharp midline frontal delineation. In the medical literature, this phenomenon was depicted under many names, including “segmental pigmentation anomaly”, “segmental naevus depigmentosus”, “giant café-au-lait macule”, “patterned dyspigmentation”, “pigmentary mosaicism” and more (2–5). In 2010 Hogeling & Frieden (6) further broadened the definition of the term SPD, to include the informa-

SIGNIFICANCE

This study supports the assumption of segmental pigmentation disorder being a solely cutaneous disorder, without any obligatory association of extracutaneous manifestations, which may diminish the need for long-term neurological follow-up and alleviate the burden felt by the child's parents when informed of the diagnosis and its possible outcomes.

tion that the pigmented patch can assume a segmental, dermatomal or chequerboard pattern (7).

Several factors have been suggested to account for the unique appearance of SPD, including the effect of neural and hormonal factors on pigment cells, somatic mosaicism and cellular chimerism (7–10).

Skin pigmentation develops in a mediolateral direction and does not cross the linea alba. Aberrant pigment dispersion is expected to lead to an irregular excess or lack of pigment, for the most part only on 1 side, a fact which may explain the sharp midline border typical of SPD (1).

SPD is usually sporadic, although familial cases have been reported (1, 6). Paradominant inheritance may explain familial cases: an individual heterozygous for a paradominant mutation has a normal phenotype, thus the mutant allele can be passed on to future generations without being phenotypically discernible, unless a somatic mutation appears at an early stage of embryonic development, causing loss of heterozygosity and forming a homozygous subpopulation of cells. This results in a mosaic phenotype comprising 2 subsets of cell populations; homo and heterozygous. Once the skin development in the foetus is completed, paradominant features can no longer be expressed (7).

SPD appears during infancy and is characterized by a small number of lesions distributed segmentally, typically involving the frontal torso. The midline border is predominantly frontal and sharp, and the lateral border is less salient. The SPD lesions may cross the midline; however, by no more than a few centimetres (6) and tend to fade over time (1) (although pigmentation may persist into adulthood; 2, 6). SPD has not been found to be convincingly associated with extracutaneous manifestations (1, 6). Atrial septal defect (ASD), strabismus with retinal

hypopigmentation, and bronchogenic cyst have been reported in patients with SPD and other mosaic-patterned pigmentation disorders, but it is not clear to what extent this association reflects a causal relationship (6, 11).

Hyperpigmented SPD lesions are characterized histologically by a higher amount of melanin than usual in the stratum basale due to an increased production (1), similarly to histological findings reported in café au lait spots (12). Hypopigmented lesions show less melanin than usual, but the number of melanocytes is normal or reduced (13–15).

The differential diagnosis of hyperpigmented lesions include giant café-au-lait macules (2, 3, 6, 16), McCune-Albright syndrome (17–19), speckled lentiginous naevi (20), naevoid hyperpigmentation (6, 21), congenital pigmented naevus (22–26), congenital giant Becker's naevus (27, 28) and segmental neurofibromatosis (2, 29). The differential diagnosis of hypopigmented SPD (30) spans segmental vitiligo (6), naevus anaemicus (21), tuberous sclerosis (32) and naevoid hypopigmentation, such as hypomelanosis of Ito (11, 21).

SPD is likely to be more common than reported in the literature.

The aim of this study was to systematically characterize the clinical features of SPD in a large cohort of affected children to establish whether the diagnosis of SPD requires further medical investigations or follow-up.

MATERIALS AND METHODS

Study population

This was a retrospective case-control study. A total of 185 subjects were diagnosed with SPD at 2 medical centres in Israel: 145 patients who were evaluated at the Children's Dermatology Clinic at Schneider Medical Center between the years 1975 and 1995, and 40 patients evaluated at the Tel-Aviv Sourasky Medical Center between 1995 and 2012. SPD was defined as a hypo- or hyper-pigmented patch in a segmental distribution with a well-defined midline demarcation first distinguished in early infancy. Patients with other defined pigmentary disorders were excluded, such as giant café-au-lait macules (round or oval patches, which lack the characteristic midline demarcation and segmental distribution) (2, 3, 6, 16), McCune-Albright syndrome (multiple hyperpigmented macules/patches following Blaschko's lines with additional characteristic systemic manifestations as precocious puberty and polyostotic fibrous dysplasia) (17–19), naevoid hyperpigmentation (multiple whorled hyperpigmented patches along Blaschko's lines) (6, 21), segmental neurofibromatosis (discrete oval or round hyperpigmented macules expressed with additional findings, as axillary and intertriginous freckling and neurofibromas) (2, 29), segmental vitiligo (depigmented well-defined macules) (6), etc.

The control group consisted of subjects who visited the 2 centres during the same years

because of other skin disorders, not associated with neurological manifestations, including atopic dermatitis, hyperhidrosis, keratosis pilaris, dyshidrotic eczema, and seborrhoeic dermatitis. The subjects were paired according to age and sex.

Data were collected from the patients' digital medical records, handwritten medical charts, photographed slides of physical findings at baseline (enabling further clinical description of the pigmentation characteristics at time of diagnosis) and a phone interview. Data collected included demographic details (sex, age at presentation and at follow-up); ethnic background (ethnic origin was defined based on the origin of 2 or more grandparents); clinical details including characteristics and changes in size over time of the pigmented patch (based on medical records, charts, interviews and photographs), family history, additional cutaneous and extracutaneous manifestations, and evaluation of personal and social coping extracted from the telephone questionnaire.

Data analysis

Continuous variables were described using a mean and standard deviation (SD); continuous variables that did not fit a normal distribution were described using a median and interquartile range (IQR). Categorical variables were presented using frequency and percentages. A univariate analysis was used to compare the demographic data, the additional skin phenomena, the family history, and the existence of extracutaneous manifestations. The Pearson χ^2 test and the Fisher's exact test were used to compare the categorical variables between the study and control groups. The 2-sample Wilcoxon test was used to compare the continuous variables among the 2 groups. When the results of all the tests for categorical variables that consisted of more than 3 categories were significant, pairwise comparisons were performed. The false discovery rate method was used to match the level of significance. Differences were determined as significant when the *p*-value was less than 0.05. The statistical analysis of the data was performed using SAS system for Windows (SAS Institute Inc., Cary, NC, USA).

RESULTS

A total of 185 subjects were diagnosed with SPD, of which 144 individuals had accessible medical records,

Table I. Demographic characteristics

Variable	Study group <i>n</i> (%)	Control group <i>n</i> (%)	<i>p</i> -value
Age group ^a			0.97
Child (0–10 years)	7 (5)	7 (5)	
Adolescent (11–18 years)	8 (6)	7 (5)	
Young adult (19–24 years)	8 (6)	6 (4)	
Adult (25–42 years)	109 (76)	110 (76)	
Middle age (43 years and up)	12 (8)	14 (10)	
Age of onset, years, median (min, max) ^b	0 (0, 11)		
Age at time of examination, years, median (min, max) ^c	2.0 (0.0, 23.0)	4.0 (0.0, 23.0)	0.033
Period of follow-up, years, median (min, max) ^c	27.0 (5.0, 40.0)	27.0 (6.0, 36.0)	0.97
Sex ^a			1.00
Male	58 (40)	58 (40)	
Female	86 (60)	86 (60)	
Origin ^d			0.045
Sephardic Jewish	39 (51)	14 (39)	
Ashkenazi Jewish	20 (26)	6 (17)	
Mixed Jewish	6 (17)	20 (26)	
Israeli	5 (7)	1 (3)	
Arab	0 (0)	2 (6)	
Other	2 (3)	3 (8)	

Data was available for ^a144 patients (100%) in each of the control and study group, ^b71 patients (49%) in the study group, ^c119 patients (83%) and 101 patients (70%) in the control and study group, respectively and ^d76 patients (53%) and 36 patients (25%) in the control and study group, respectively.

thus comprising the study group; the control group consisted of 144 subjects diagnosed with atopic dermatitis ($n=112$, 78%), bullous impetigo ($n=13$, 9%), hyperhidrosis ($n=15$, 10%), keratosis pilaris, dyshidrotic eczema, seborrhoeic dermatitis and molluscum contagiosum (1 of each, total 3%).

Comparative demographic data are shown in **Table I**. The groups were paired according to age and sex (p -value not indicating variance for both). Variance was ascertained based on age at examination and ethnic origin (a statistically significant p -value). Most patients were adults 25–42 years (76% in each group), females (60%) and of Sephardic Jewish origin. The median age of onset of SPD is close to birth, with a mean of 1.33 years.

Table II presents the clinical characteristics of the pigmentation. Most of the pigmentary lesions were distributed across several anatomical locations (44%, most often with torso involvement) or located solely on the torso (43%), and were hypopigmented patches (52%), with a frontal demarcation midline (61%) and no clear predilection to ill- (48%) or well-defined (47%) borders (**Fig. 1**). Throughout the years the pigmentation size and intensity remained unchanged in 41% and 55% of cases, respectively. Ninety-five percent of SPD patients did develop additional cutaneous manifestations. Most SPD patients did not have a first-degree relative diagnosed with SPD (89%), though 2 patients had a sibling with SPD (7%) and 1 affected individual had a parent diagnosed with SPD (4%).

SPD was asymptomatic in all patients. Data regarding personal coping were based on 28 patients with up-to-date contact details who completed a telephone questionnaire. Most SPD patients did not report any aesthetic concern (64%) or impairment of quality of life (89%), whereas half of the subjects reported experiencing social consequences, such as negative remarks and a sense of embarrassment.

No differences in family medical history, personal morbidity, medications and neurological manifestations

Table II. Clinical characteristics of segmental pigmentation disorder (SPD)

Variable	n (%)
Location	129 (90)
Torso	56 (43)
Head and neck	9 (7)
Limbs	7 (5)
Multiple areas	57 (44)
Type of pigmentation	120 (83)
Hypopigmentation	62 (52)
Hyperpigmentation	48 (40)
Mixed	10 (8)
Midline	124 (86)
Frontal	76 (61)
Dorsal	26 (21)
Mixed	22 (18)
Borders	100 (70)
Ill-defined	48 (48)
Well-defined	47 (47)
Mixed	5 (5)
Change in size	29 (20)
Unchanged	1 (41)
Proportionate to growth	9 (31)
Disappeared	4 (14)
Decreased	2 (7)
Increased disproportionate to growth	2 (7)
Change in intensity	29 (20)
Unchanged	1 (55)
Lightened	5 (17)
Disappeared	4 (14)
Darkened	2 (7)
Other ^a	2 (7)
Additional cutaneous morbidity	144 (100)
None	137 (95)
Atopic dermatitis	3 (2)
Other ^b	4 (3)
SPD in first-degree relatives	28 (19)
None	25 (89)
Sibling	2 (7)
Parent	1 (4)

^aOne subject noted that the light marks remained unchanged, whereas the dark marks became more salient. An additional subject noted that, over time, freckles appeared onto the surface of the existing pigmentation mark. ^bContact dermatitis, pigmentation and pruritus during pregnancy, capillary haemangioma, and seborrhoea.

were found between the 2 groups. Family history and co-morbidities among patients with SPD and control individuals are listed in Table SI.

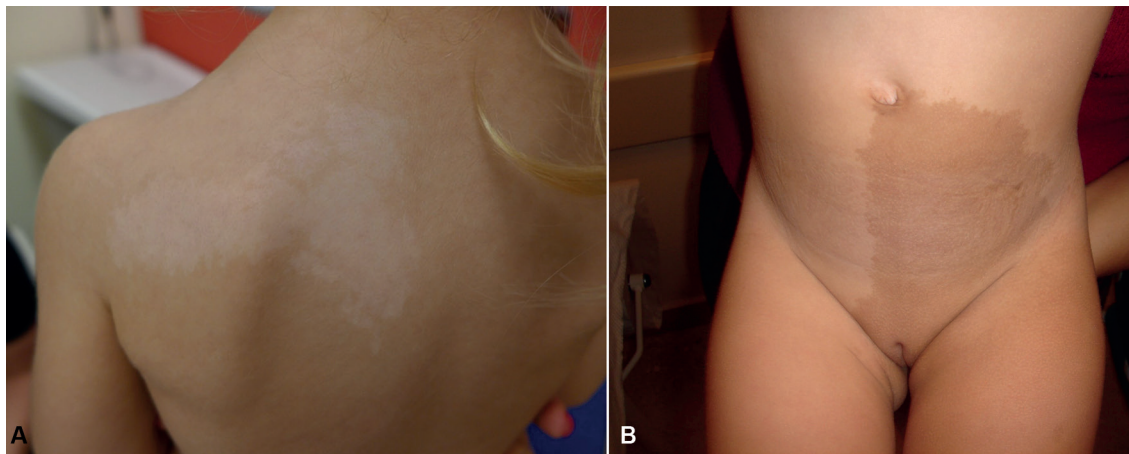


Fig. 1. (A) A female child diagnosed with segmental pigmentation disorder (SPD) demonstrates a unilateral hypopigmented patch demarcated at the midline of the left upper back. (B) A toddler with a hyperpigmented patch with sharp borders on the lower abdomen and genitalia.

DISCUSSION

This study of a large cohort of patients comprehensively delineated the demographic, cutaneous and extracutaneous manifestations of SPD over a long period of follow-up. **Table III** compares the principal findings of the current study with the available literature. SPD is first expressed near birth (median age 0); previous studies suggested that the pigmentation appears slightly after birth, but is not evident immediately at birth, due to the infant's skin's initial predisposition to hypopigmentation and its lack of exposure to the sun (13, 14). Consistent with previous data (1, 6), the current study could not identify any sex predominance.

SPD tends to manifest in children with dark skin (1, 6). This may be consistent with the fact that most of the patients in the current series were of Sephardic origin, as reported in a previous study (1).

The current study shows that SPD commonly involves the torso. This finding is in agreement with the observations of both Metzker (1) and Hogeling & Frieden (6), who found that the most common locations of SPD in an ascending order were the back, chest, and abdomen.

Slightly more than half of the patients had hypopigmentary patches (52%). Similarly, Metzker (1) found that 50% of subjects with SPD display hypopigmented lesions. In contrast, Hogeling & Frieden (6) report hyperpigmentation in 77% of patients with SPD.

The current study found no significant differences regarding ill- vs well-defined borders. The lesion midline border was mostly frontal; Hogeling & Frieden (6) also found a frontal midline in most of their patients (82%).

Previous studies showed that pigmentation tends to fade over the years (1), but could persist throughout adulthood. Hogeling & Frieden (6) described 2 adults with SPD. Orion et al. (2) described a series of cases in which the pigmentation did not fade over time. The

current study suggests that pigmentation intensity or size do not change over the years.

In accordance with the literature, SPD was found to be asymptomatic (1, 6). In addition, the psychological impact of SPD was ascertained here for the first time to the best of our knowledge. No significant deleterious effect was observed, although half of the subjects experienced negative social remarks.

A first-degree relative with SPD was found in only 3 cases (11%), which could be explained by the mechanism of paradominant inheritance (33).

Extracutaneous findings have been related in the past to mosaic-patterned pigmentation disorders, such as hypomelanosis of Ito and linear and whorled hypermelanosis, including neural, ocular and cardiac manifestations (11). Similarly, cases of naevus depigmentosus accompanied by disorders of the central nervous system were described: Kim et al. (14) described a case of localized naevus depigmentosus with seizures (1 out of 60 subjects), out of which 32 patients had a segmental picture that may matched SPD, and Nehal et al. (36) described one subject with systemic manifestations out of 9 with segmental naevus depigmentosus. In most cases of naevus depigmentosus there are no systemic extracutaneous manifestations, and, in particular, no neurological manifestations (11, 14, 15, 37). In the current study, most of the subjects were healthy, and co-morbidities were not significantly associated with SPD, as previously found (6).

Study limitations

This study was limited by its retrospective design. In addition, some of the data had been collected through a questionnaire, suggesting the possibility of a recall bias. Data regarding personal consequences of the pigmentary disorder were based solely on the telephone questionnaire fulfilled by 20% of patients, thus withholding an incomplete data bias.

Table III. Comparative analysis of segmental pigmentation disorder (SPD) features in this and previous studies

Parameter	Current study	Previous study	Correlation
Demographic characteristics			
Age of onset	Near birth	Near birth, during infancy (1, 6)	+
Sex	No predominance	No predominance	+
Origin	Sephardic	More in frequent in Fitzpatrick type III and up (1, 6)	Indirect
Characteristics of the pigmentary spot			
Common location	Torso (primary site or as part of a wider distribution)	Torso (1, 6)	+
Type of pigmentation	Hypo or hyperpigmented patches	Hypo- or hyper-pigmented patches	+
Midline	Frontal	The midline border is predominantly frontal and sharp, the lateral border is less salient (1, 6)	+/-
Border's accentuation	No predilection		
Changes in size and intensity over the years	Unchanged	Tends to fade over the years but can persist (1, 2, 6)	+/-
Personal coping			
Accompanying symptoms	None	None (1, 6)	+
Quality of life impairment	None	Unknown	
Social consequences	Described by half of the patients		
Familial predisposition to SPD	Three of the subjects had a first-degree relative with SPD	SPD appears sporadically, although there may be familial cases (1, 6)	+
Additional dermatoses	None	None (1, 6)	+
Extracutaneous manifestations	No association	No association (1, 6)	+

Conclusion

SPD tends to manifest during the first year of life, it is more common among children of Sephardic origin, is rarely familial, and consists of hypo- or hyper-pigmented asymptomatic patches, most often located on the torso, with a frontal midline, which can persist into adulthood. SPD is not associated with extracutaneous manifestations; an observation that carries obvious implications for the counselling of patients with SPD and their families.

The authors have no conflicts of interest to declare.

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