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Childhood-onset psoriasis: association with future cardiovascular and metabolic comorbidities

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Summary

Background Psoriasis is associated with higher prevalences of cardiovascular and metabolic comorbidities in adults but the relationship of age at onset and those prevalences is unknown.
Objective To evaluate whether the childhood onset of psoriasis (COP) is correlated with the frequency of cardiovascular and metabolic comorbidities in adulthood.
Methods This noninterventional, cross-sectional, multicentre study of adults with psoriasis was conducted in 29 dermatology centres in France. Data on sex, age at onset of psoriasis and its clinical characteristics, and cardiovascular risk factors, including weight, body mass index, waist circumference, dyslipidaemia, diabetes, hypertension, smoking, and personal/familial major adverse cardiovascular events (MACE) were systematically recorded.
Results Two thousand two hundred and one patients with psoriasis (male: 56%; mean age: 49 years; 25% with COP) were included consecutively in the study. Univariate analysis showed that COP was associated with lower frequencies of obesity, high waist circumference, diabetes, dyslipidaemia, hypertension, familial cardiovascular disease, MACE and metabolic syndrome, but more frequent active smoking. Multivariate analysis retained age as being associated with frequency of cardiovascular and metabolic comorbidities, and sex with smoking, but not age at the onset of psoriasis. Psoriasis severity was associated with higher frequencies of obesity and psoriatic arthritis.
Conclusion Our results showed that COP does not seem to be an additional risk factor for higher frequencies of cardiovascular and metabolic comorbidities during adulthood.

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What's already known about this topic?

- Psoriasis and its severity are associated with higher prevalence of cardiovascular and metabolic comorbidities in adults.
- Childhood onset of psoriasis is not associated with obesity in adulthood.

What does this study add?

- Childhood onset of psoriasis is not associated with cardiovascular and metabolic comorbidities in adulthood.
- In France, as in most countries, psoriasis is associated with high frequencies of cardiovascular and metabolic comorbidities in adults.

Psoriasis is a chronic immune-mediated inflammatory disorder affecting 2–3% of the white population in western countries.[1] During the past decade, cardiovascular, i.e. hypertension, coronary diseases, major cardiovascular events (MACE), and metabolic, i.e. obesity, abnormal plasma lipid metabolism, and insulin resistance, comorbidities have been associated with psoriasis.[2–8] Smoking and parental cardiovascular diseases, two major risk factors for cardiovascular diseases, are also associated with psoriasis.[9–11] The notion of a psoriatic march is debated.[8,12–15] The hypothesis of an aetiological role of psoriasis in cardiovascular and metabolic diseases is supported by pathogenic concepts establishing a link between chronic inflammation in psoriasis, insulin resistance, endothelial cell dysfunction and atherosclerosis.[12,16–19]

The childhood onset of psoriasis (COP) is relatively common. According to the literature, 35–50% of patients with psoriasis have the disease before the age of 20 years[1,20–22] and in Europe about 1% of children are affected.[14,23] Some studies also show that children with psoriasis have higher risks for cardiovascular and metabolic comorbidities.[23,24] Little information is available about the link between COP and cardiovascular and metabolic diseases in adulthood. Recently the authors of one study found that COP did not influence future body mass index (BMI).[25]

Therefore, we conducted a multicentre cross-sectional study to evaluate the potential relationship between age at the onset of psoriasis and the patients' frequencies of cardiovascular risk factors, and cardiovascular and metabolic diseases during adulthood.

Methods

This noninterventional, cross-sectional, multicentre study of adults with psoriasis was performed in 29 dermatology centres in France from 15 June to 31 October 2011. COP was defined as disease onset before the age of 18 years, and adult-onset psoriasis (AOP) as disease onset after 18 years.

Investigative centres

Twenty-nine dermatological centres throughout France, members of Resopso, participated in this study. Resopso (http://resopso.fr) is an association of French dermatologists involved in the care of patients with psoriasis. These 29 centres were in university ($n = 9$), general ($n = 11$) and military hospitals ($n = 2$), and with private practitioners ($n = 7$). Seven had clinics dedicated to patients with psoriasis.

Patient evaluation

All patients with psoriasis who had a consultation during the 4·5 months of the study in the 29 centres were included in the study. A protocol for evaluation was implemented with a case report form especially created for the study. It comprised 38 items, including data on patients (i.e. age, sex); psoriasis (i.e. age at onset, clinical characteristics, rheumatism, history of treatments, family history including first-degree relatives only); cardiovascular risk factors and diseases (i.e. hypertension, current smoking, MACE (including angina pectoris, myocardial infarction and stroke) and family history of MACE (including myocardial infarction, cardiac death and stroke in first-degree relatives); and metabolic diseases (i.e. weight, BMI calculated as weight in kg divided by height in m^2, waist circumference, diabetes and dyslipidaemia).

Overweight was defined as a BMI > 25 kg m^{-2}, and obesity as BMI > 30 kg m^{-2}.[26,27] Diabetes mellitus was diagnosed when patients had a fasting glycaemia ≥ 7 mmol L^{-1} ($1{\cdot}26$ mg L^{-1}), or reported the use of oral glucose-lowering medication or insulin. Participants were classified as having hypertension when their systolic blood pressure was ≥ 140 mmHg or diastolic blood pressure was ≥ 90 mmHg, or they reported taking blood pressure-lowering medication. Dyslipidaemia was defined as low-density lipoprotein cholesterol levels ≥ 160 mg dL^{-1} ($4{\cdot}14$ mmol L^{-1}), high-density lipoprotein cholesterol levels < 40 mg dL^{-1} ($1{\cdot}03$ mmol L^{-1}), and triglyceride levels ≥ 200 mg dL^{-1} ($2{\cdot}26$ mmol L^{-1}).

Subjects taking lipid-lowering medication were also classified as having dyslipidaemia. A current smoker was defined as consuming ≥ 5 cigarettes per day for at least 1 year. Metabolic syndrome was diagnosed for patients with three of the following four criteria: waist circumference > 80 cm for females and 94 cm for males (European reference for waist circumference) or BMI ≥ 30 kg m^{-2}; diabetes mellitus; hypertension; and dyslipidaemia.[28] Severe psoriasis corresponds to those patients receiving traditional systemic treatment (i.e. acitretin, methotrexate, ciclosporin) or a biologic, on the day of inclusion in the study.

Statistical analysis

Quantitative data are expressed as means ± standard deviation (SD), qualitative data as n (%). Means were compared using Student's t-test and frequencies with the χ^2 test or Fisher's exact test when necessary. Multiple regression analysis was used to evaluate the relationship between risk factors and the features of psoriasis, the latter being those achieving $P < 0{\cdot}05$ in univariate analysis. Because of multiple comparisons a Bonferroni adjustment was performed. A P value < 0·001 was considered as statistically significant. Statistical analyses were computed with SAS software v 9.3 (SAS Institute Inc., Cary, NC, U.S.A.).

Results

Among the 2255 psoriatic patients seen in the 29 dermatology centres, 54 were not included because they were < 18 years old at inclusion (n = 5), no information was available about age at inclusion or age at onset of psoriasis (n = 18), or they were duplicates (n = 31). Finally 2201 patients were included.

Patients and the characteristics of psoriasis

The patients' mean age at inclusion was 49 (range 18–97) years and 56% were men (Table 1). The mean age at onset of psoriasis was 31 (range 0–92) years. For 25% of patients, the first signs of the disease occurred before the age of 18 years and this was more frequently seen in women. The mean duration of psoriasis was 18 (range 0–81) years. Affected first-degree relatives were: 25% of parents, 15% of siblings, and 7% of children. Plaque psoriasis was the predominant type, and it occurred significantly more often in males. Other characteristics of these patients and their disease are reported in Table 1.

About one-third of the patients were taking traditional systemic treatments (i.e. acitretin, ciclosporin or methotrexate) on the day of inclusion, and approximately one quarter received a biologic (i.e. etanercept, adalimumab, infliximab or ustekinumab).

Compared with patients with AOP, those with COP were significantly younger. Their mean duration of psoriasis was significantly longer, they had significantly more frequent familial disease, plaque psoriasis, and were more often on treatment with a biologic, but less often on traditional systemic therapy.

Cardiovascular and metabolic diseases

Patients with psoriasis were frequently overweight (including obesity) (58%), diabetic (11%), dyslipidaemic (28%), hypertensive (26%), smokers (33%), and had a familial cardiovascular disease history (24%) (Table 2). The metabolic syndrome was diagnosed in 15% of the patients, and 7% suffered from MACE. Compared with women, men were significantly more often overweight or obese, dyslipidaemic, hypertensive, current smokers and had MACE.

According to our univariate analysis, comparing COP vs. AOP patients, patients with COP weighed significantly less, with significantly lower BMI, waist circumference, and frequency of overweight and obesity, diabetes, dyslipidaemia, hypertension and family history of cardiovascular diseases, but they were more frequently smokers. MACE and metabolic syndrome showed similar tendencies, being significantly more frequent in AOP patients than in COP subjects.

Multivariate analyses

Our multivariate analyses (Table 3) retained age as significantly associated with waist circumference, and higher frequencies of obesity, diabetes, dyslipidaemia, hypertension and psoriatic arthritis with a lower percentage of smokers. Also there was a significantly higher frequency of smokers among males. These analyses showed the severity of psoriasis to be significantly associated with a higher frequency of obesity and psoriatic arthritis. Finally, age at the onset of psoriasis had no effect on the frequencies of metabolic and cardiovascular comorbidities.

Discussion

This multicentre study of 2201 French patients with psoriasis was undertaken to examine the potential relationship between age at the onset of psoriasis on the frequencies of cardiovascular and metabolic comorbidities in adulthood. Our results showed, in accordance with an earlier report that found COP to have no influence on the frequency of obesity in adulthood,[25] that age at onset was not associated with adult frequencies of comorbidities. Finally, the only parameter that modified frequencies of comorbidities was the age of the patient, with the exception of smoking for which male gender was an independent parameter associated with a higher frequency of smoking.

Comparing COP with AOP provided more information on the relationship between the age at onset of psoriasis and the disease course. Consistent with earlier studies, COP was more frequent in girls,[22,25,29] and was associated with a family history of psoriasis,[20,22,29,30] but not with joint involvement.[29–31] Our findings also showed that age at the onset of psoriasis had no relationship with disease severity. No consensus has been

Table 1 Clinical characteristics at inclusion of the 2201 psoriasis patients according to sex, age at onset and disease duration (univariate analysis)

		Sex			Age at onset of psoriasis		
Characteristic	All patients n = 2201	Male n = 1240	Female n = 961	P-value	COP[a] n = 545	AOP[a] n = 1656	P-value
Age (years), mean ± SD	48·7 ± 15·5	48·7 ± 14·5	48·6 ± 16·6	NS	39·1 ± 13·5	51·8 ± 14·8	< 0·0001
Sex, male/female	1240/961	NA	NA	NA	260/285	980/676	< 0·0001
Age (years) at onset of psoriasis, mean ± SD	31·1 ± 17·5	31·3 ± 16·3	30·9 ± 18·8	NS	11·6 ± 4·4	37·5 ± 15·3	NA
Onset before 18 years, n (%)	545 (24·8)	260 (21·0)	285 (29·7)	< 0·0001	545 (100)	0	NA
Psoriasis duration (years), mean ± SD	17·6 ± 13·7	17·4 ± 13·1	17·7 ± 14·5	NS	27·5 ± 13·7	14·3 ± 12·0	< 0·0001
Familial psoriasis, n (%)[b]	867 (40·0)	481 (39·5)	386 (40·8)	NS	293 (54·7)	574 (35·2)	< 0·0001
Plaque psoriasis, n (%)	1633 (78·9)	990 (85·1)	643 (71·1)	< 0·0001	449 (87·2)	1184 (76·2)	< 0·0001
Joint involvement, n (%)	419 (21·5)	221 (20·2)	198 (23·2)	NS	96 (19·9)	323 (22·0)	NS
Treatment of psoriasis, n (%)							
None	111 (5·3)	61 (5·2)	50 (5·5)	0·0007	26 (5·1)	85 (5·4)	< 0·0001
Topical	940 (44·8)	500 (42·3)	440 (48·0)		186 (36·2)	754 (47·6)	
Phototherapy	85 (4·0)	54 (4·6)	31 (3·4)		21 (4·1)	64 (4·0)	
Traditional systemic	747 (35·6)	411 (34·8)	336 (36·6)		163 (31·7)	584 (36·8)	
Biologic	683 (32·5)	432 (36·5)	251 (27·4)		206 (40·1)	477 (30·1)	
Severe psoriasis, n (%)[c]	1437 (65·3)	848 (68·4)	589 (61·3)	0·0005	374 (68·6)	1063 (64·2)	NS

NS, not significant; NA, not applicable. [a]Childhood-onset psoriasis (COP) was defined as disease onset before the age of 18 years, and patients with adult-onset psoriasis (AOP) as disease onset after 18 years. [b]Familial psoriasis was defined as psoriasis occurring in first-degree relatives: parents (n = 550), brothers/sisters (n = 329), and/or children (n = 147). [c]Severe psoriasis corresponds to patients receiving traditional systemic treatment (i.e. acitretin, methotrexate, ciclosporin), or a biologic the day of inclusion in the study.

Table 2 Cardiovascular disease, its risk factors and metabolic diseases according to sex, age at psoriasis onset and its duration (univariate analysis)

		Sex			Age at psoriasis onset		
Characteristics	All the patients n = 2201	Male n = 1240	Female n = 961	P-value	COP[a] n = 545	AOP[a] n = 1656	P-value
Weight (kg), mean ± SD	77·7 ± 18·0	83·6 ± 16·4	70·0 ± 17·0	< 0·0001	74·2 ± 17·8	78·8 ± 17·9	< 0·0001
BMI (kg m^{-2}), mean ± SD	27·0 ± 5·8	27·3 ± 5·1	26·7 ± 6·5	NS	25·8 ± 5·8	27·4 ± 5·7	< 0·0001
< 25, n (%)	917 (42·0)	443 (36·0)	474 (49·7)	< 0·0001	280 (51·8)	637 (38·7)	< 0·0001
25–29·9, n (%)	734 (33·6)	495 (40·2)	239 (25·1)		164 (30·3)	570 (34·7)	
≥ 30, n (%)	534 (24·4)	294 (23·9)	240 (25·2)		97 (17·9)	437 (26·6)	
Waist circumference (cm), mean ± SD	95·9 ± 16·0	98·5 ± 15·0	92·5 ± 16·6	< 0·0001	91·5 ± 15·7	97·3 ± 15·9	< 0·0001
Diabetes, n (%)	238 (10·9)	135 (11·0)	103 (10·7)	NS	25 (4·6)	213 (12·9)	< 0·0001
Dyslipidaemia, n (%)	599 (27·5)	378 (30·8)	221 (23·2)	< 0·0001	89 (16·4)	510 (31·1)	< 0·0001
Hypertension, n (%)	570 (26·0)	342 (27·7)	228 (23·8)	NS	68 (12·5)	502 (30·5)	< 0·0001
Smoking, n (%)	712 (32·6)	421 (34·3)	291 (30·4)	NS	205 (37·8)	507 (30·9)	NS
Familial cardiovascular history, n (%)	508 (24·4)	281 (24·1)	227 (24·6)	NS	99 (18·9)	409 (26·2)	< 0·0001
MACE, n (%)	143 (6·5)	98 (7·9)	45 (4·7)	NS	14 (2·6)	129 (7·8)	< 0·0001
Angina pectoris	63 (2·9)	44 (3·6)	19 (2·0)	NS	7 (1·3)	56 (3·4)	NS
Myocardial infarction	56 (2·5)	41 (3·3)	15 (1·6)	NS	8 (1·5)	48 (2·9)	NS
Stroke	40 (1·8)	26 (2·1)	14 (1·5)	NS	2 (0·4)	38 (2·3)	NS
Metabolic syndrome, n (%)	318 (15·3)	186 (15·9)	132 (14·6)	NS	39 (7·6)	279 (17·8)	< 0·0001

NS, not significant; BMI, body mass index; MACE, major adverse cardiovascular events. [a]Childhood-onset psoriasis (COP) was defined as disease onset before the age of 18 years, and patients with adult-onset psoriasis (AOP) as disease onset after 18 years.

reached on whether the onset of psoriasis during childhood predicts milder or more severe disease. Some authors found early onset to be associated with greater severity,[29–31] while others reported no influence of age at onset.[25,29] The use of different definitions of early psoriasis or COP and the criteria of severity evaluated [body surface area (BSA), Psoriasis Area and Severity Index (PASI), use of systemic treatment] could explain these differences. For example biologics were prescribed more frequently for patients with COP in our study, probably because of French regulations about their use. The authorization to use

Table 3 Multivariate analysis

Risk factors Psoriasis features	Univariate analysis P-value	Multivariate analysis P-value	 OR (95% CI)
Obesity ($\geq$ 30 kg m^{-2})			
Patient age	< 0·0001	< 0·0001	1·03 (1·02–1·04)
Patient sex	< 0·0001	0·40	–
Age at onset (COP vs. AOP)[a]	< 0·0001	0·37	–
Psoriasis severity[b]	0·0009	< 0·0001	1·56 (1·26–1·98)
Waist circumference			
Patient age	< 0·0001	< 0·0001	1·04 (1·03–1·05)
Patient sex	< 0·0001	0·89	–
Age at onset (COP vs. AOP)[a]	< 0·0001	0·81	–
Psoriasis severity[b]	0·001	0·15	–
Diabetes			
Patient age	< 0·0001	< 0·0001	1·06 (1·05–1·07)
Patient sex	0·66	0·40	–
Age at onset (COP vs. AOP)[a]	< 0·0001	0·11	–
Psoriasis severity[b]	0·65	0·15	–
Dyslipidaemia			
Patient age	< 0·0001	< 0·0001	1·06 (1·05–1·07)
Patient sex	< 0·0001	0·40	–
Age at onset (COP vs. AOP)[a]	< 0·0001	0·11	–
Psoriasis severity[b]	0·65	0·15	–
Hypertension			
Patient age	< 0·0001	< 0·0001	1·08 (1·07–1·10)
Patient sex	0·05	0·005	–
Age at onset (COP vs. AOP)[a]	< 0·0001	0·36	–
Psoriasis severity[b]	0·74	0·08	–
Smoking			
Patient age	< 0·0001	< 0·0001	1·01 (1·007–1·02)
Patient sex	0·04	< 0·0001	1·96 (1·64–2·34)
Age at onset (COP vs. AOP)[a]	0·003	0·23	–
Psoriasis severity[b]	0·003	0·25	–
Psoriasis arthritis			
Patient age	0·001	0·004	–
Patient sex	0·10	0·04	–
Age at onset (COP vs. AOP)[a]	0·35	0·74	–
Psoriasis severity[b]	< 0·0001	< 0·0001	2·33 (1·79–3·02)

OR, odds ratio; CI, confidence interval. [a]Childhood onset psoriasis (COP) was defined as disease onset before the age of 18 years, and patients with adult-onset psoriasis (AOP) as disease onset after 18 years. [b]Severe psoriasis corresponds to patients receiving traditional systemic treatment (i.e. acitretin, methotrexate, ciclosporin), or a biologic the day of inclusion in the study.

a biologic requires the prior administration of at least two conventional systemic treatments, including phototherapy.

Cardiovascular and metabolic comorbidities were very frequent in our population, compared with the French general population. Although our study was not designed to evaluate the frequencies of comorbidities in comparison with the general population, they can be compared with values from databases on the French general population. In 2009, a large cross-sectional study designed to evaluate the frequencies of obesity and comorbidities in 25 286 persons,[32] estimated an obesity rate of 15% for the general population $\geq$ 18 years old. In our study this frequency was higher, 24%. Even if the general population is not strictly comparable for age and sex with our patients with psoriasis, the latter's frequencies were a little higher than those of the general French population, respectively, for hypertension (26% vs. 18%), diabetes (11% vs. 5%), dyslipidaemia (28% vs. 15%) and current smokers (33% vs. 19%).

Of emerging importance is the relationship between cardiovascular and metabolic diseases, and chronic severe psoriasis in adults and children.[33–35] It could explain the higher mortality of patients with severe psoriasis.[2,36,37] However, evaluating the relationship between the severity of psoriasis, its long-term evolution and comorbidities seems quite difficult and open to debate.[14,37] Firstly, severe psoriasis may refer to clinical disease activity and the extent of the lesions as assessed by PASI or BSA as involved;[38] the impact of quality of life, i.e. determination of the Dermatology Life Quality Index score which is not always correlated with clinical severity; some unusual severe forms of psoriasis, such as acrodermatitis; or finally, all patients with psoriasis who require systemic treatment or phototherapy, at any time. Secondly, it is not yet possible to predict the long-term outcome and prognosis of COP, in the absence of prospective long-term evaluation of these children. So, severe psoriasis in childhood can become moderate or mild in adulthood and *vice versa*. Finally, psoriasis is a dynamic disease. Although some patients with psoriasis have long-term severe disease, others have transient severe disease, e.g. sometimes triggered by stress, infections or pregnancy. These acute forms satisfy all the criteria of severe disease, but last only for a few months.

The question we asked here was whether COP could be associated with a higher risk of cardiovascular and metabolic comorbidities, independently of severity, in adulthood. Because of the study design (i.e. a cross-sectional study on adults with active psoriasis), transient psoriasis in childhood, like napkin psoriasis or guttate psoriasis, was excluded from the study. We included all patients with psoriasis, regardless of their disease severity, and considered as severe in the multivariate analysis only those receiving systemic treatment or a biologic on the day of inclusion. Probably because patients consulted dedicated psoriasis centres mostly in hospitals, two-thirds of the patients met the criteria for severe psoriasis. In any case, neither age at onset nor disease duration was associated with the frequency of cardiovascular and metabolic comorbidities in adulthood.

The psoriatic march tries to explain the potential link between psoriasis and, more generally, chronic inflammatory diseases, like Crohn disease and rheumatoid arthritis, and the high frequencies of cardiovascular events associated with these entities. Systemic inflammation can cause insulin resistance, which, in turn, induces endothelial cell dysfunction, leading

to atherosclerosis and, eventually, to myocardial infarction or stroke.[12] Therefore we hypothesized that COP might be associated with higher rates of cardiovascular and metabolic diseases; this hypothesis was not substantiated. Univariate analysis results suggested that COP protected against comorbidities, except for tobacco use, but COP patients were younger than those with AOP, and it is well known that the frequencies of diabetes, dyslipidaemia, hypertension, obesity, abdominal obesity and MACE increase with age. On the other hand, smoking decreased with age. According to our multivariate analysis, age was always significantly associated with higher percentages of all those risk factors. Sex was mainly linked to frequencies of hypertension and smoking, and the severity of psoriasis to obesity. A recent Taiwanese case–control study evaluated whether the sequence of events psoriasis and metabolic disorder onsets could affect the risk for subsequent development of cardiovascular complications.[39] Psoriasis was considered the initiator of the inflammatory march when comorbidities developed after its onset, and was a potent amplifier of pre-existing comorbidities. If psoriasis served as the initiator of inflammation, the risk of developing cardiovascular disease was lower than when it served as the amplifier of disease. Future studies should collect data on such chronological events for multivariate analyses to evaluate the true impact of age at onset.

The results of this study showed that childhood onset of psoriasis was not associated with the frequency of cardiovascular and metabolic comorbidities in adulthood, and our multivariate analysis retained the higher frequency of obesity as being significantly associated with the severity of psoriasis and psoriatic arthritis.

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