MAJOR ARTICLE

Age Is an Important Risk Factor for Onset and Sequelae of Reversal Reactions in Vietnamese Patients with Leprosy

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Background. Reversal, or type 1, leprosy reactions (T1Rs) are acute immune episodes that occur in skin and/or nerves and are the leading cause of neurological impairment in patients with leprosy. T1Rs occur mainly in patients with borderline or multibacillary leprosy, but little is known about additional risk factors.

Methods. We enrolled 337 Vietnamese patients with leprosy in our study, including 169 subjects who presented with T1Rs and 168 subjects with no history of T1Rs. A multivariate analysis was used to determine risk factors for T1R occurrence, time to T1R onset after leprosy diagnosis, and T1R sequelae after treatment.

Results. Prevalence of T1Rs was estimated to be 29.1%. Multivariate analysis identified 3 clinical features of leprosy associated with T1R occurrence. Borderline leprosy subtype (odds ratio, 6.3 [95% confidence interval, 2.9–13.7] vs. polar subtypes) was the major risk factor; 2 other risk factors were positive bacillary index and presence of >5 skin lesions. In addition, age at leprosy diagnosis was a strong independent risk factor for T1Rs (odds ratio, 2.4 [95% confidence interval, 1.3–4.4] for patients aged ⩾15 years old vs. <15 years old). We observed that T1Rs with neuritis occurred significantly earlier than pure skin-related T1Rs. Sequelae were present in 45.1% of patients who experienced T1Rs after treatment. The presence of a motor or sensory deficit at T1R onset was an independent risk factor for sequelae, as was the age at diagnosis of leprosy (odds ratio, 4.4 [95% confidence interval, 1.7–11.6] for patients ⩾20 years old vs. <20 years old).

Conclusion. In addition to specific clinical features of leprosy, age is an important risk factor for both T1R occurrence and sequelae after treatment for T1Rs.

At the end of the 1980s, there was general agreement that leprosy, a chronic infectious disease caused by *Mycobacterium leprae* infection, was a major worldwide public health problem. A leprosy elimination campaign was, therefore, initiated by the World Health Organization (WHO), and >14 million people were treated with an effective multidrug therapy regimen. Consequently, the number of recorded cases of leprosy decreased from 12 million in 1985 to 460,000 in 2004 [1, 2]. Unexpectedly, however, this very substantial decrease in prevalence has not been followed by a decrease in incidence; 407,800 new cases of leprosy were diagnosed worldwide during 2004 [1, 2]. Leprosy displays a wide spectrum of clinical manifestations, with tuberculoid and lepromatous leprosy at opposite ends of the spectrum. Tuberculoid leprosy is characterized by a specific cellular immune response that leads to well-delineated skin and neural lesions without easily detectable bacilli. Lepromatous leprosy is characterized by the absence of specific cellular immune response and extensive disseminated disease with high bacillary load in the lesions [3, 4]. In the Ridley-Jopling classification, which involves histopathological, immunological, bacteriological, and clinical criteria, these 2 polar forms of leprosy are denoted as tuberculoid (TT) and lepromatous (LL), and 3 additional intermediate, or "borderline," types are defined as borderline tuberculoid (BT), mid borderline (BB), and borderline lepromatous (BL) [5]. To

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allow for the use of simplified therapeutic guidelines, the WHO has introduced a binary coding scheme, based on clinical and bacteriological criteria, that classifies cases of leprosy as either multibacillary (MB) or paucibacillary (PB) [6].

Despite the availability of effective chemotherapy, leprosy is still a significant cause of morbidity in regions of endemicity, mainly because of the frequency of definitive nerve impairments. Leprosy reactions, which are acute episodes of immunologically mediated inflammation, are a major cause of nerve damage [7] and are classified into 2 types. Type 2 reactions are systemic inflammatory responses to the deposition of immune complexes, and are clinically characterized by dermo-hypodermal nodules (erythema nodosum) that are associated with neuritis and general signs of disease (fever, discomfort, and edema of extremities). Type 2 reactions are infrequent (they occur in <5% of leprosy patients) and occur almost exclusively in patients with BL and LL leprosy [8–12]. Type 1 reversal reactions (T1Rs) are more common and can be associated with any leprosy subtype, although they are most prevalent in patients with borderline leprosy. T1Rs typically involve sudden episodes of intense, cell-mediated immunity in skin and/or nerves. Clinical manifestations of T1Rs are inflammation of preexisting or new skin lesions and/or neuritis, sometimes associated with general signs of disease [13]. Histological examination of affected lesions shows an initial influx of mononuclear cells, associated with edema, that are responsible for skin swelling and neural compression and that evolve toward well-defined epithelio-gigantocellular granuloma and fibrosis during the final stage. Immunological studies have shown the predominance of $CD4^+$ T cells and Th1-associated cytokines—particularly, IFN-γ, IL-2, IL-12, and TNF-α—in the skin lesions and in peripheral blood samples of patients with T1Rs [4, 14–18]. Although the course of T1Rs can generally be controlled with corticosteroids [13], definitive neurological impairments persist in 30%–50% of cases [19].

The prevalence of T1Rs differs widely among different geographical and epidemiological circumstances and ranges from 6% to 67% of patients with leprosy [7–13, 20–23]. Three types of risk factors for the occurrence of T1Rs have been reported, the most commonly observed of which is leprosy subtype—that is, the borderline forms (BT, BB, and BL) according to the Ridley-Jopling classification [20, 23] or the MB form according to the WHO classification [12, 23]. A second risk factor is the extent of the clinical disease as estimated from the number of skin lesions, nerve involvement, or affected body area [9, 12]. A third, more controversial risk factor is positivity of the bacterial index (BI), which is found to be statistically significant in only 1 of 3 studies [9, 20]. Although clearly interdependent, these 3 factors have never been jointly analyzed, to our knowledge. Herein, we report the first epidemiological study of T1Rs performed among the Vietnamese population. It is also the first multivariate analysis of risk factors for occurrence, time to onset, and post-therapeutic sequelae of T1Rs in patients with leprosy.

PATIENTS AND METHODS

Patients. Patients were enrolled in the study from 1998 to 2004, as a part of a large epidemiological study performed in Ho Chi Minh City, Vietnam. All index cases were identified from the records of the Ho Chi Minh City Dermatology Hospital. Access to the registry was approved by the institutional review board of the hospital. As part of an independent genetic study, the patients were included in the study only if both of their parents were still alive. During the first period (1998–2002), we recruited patients with leprosy irrespective of the occurrence of T1Rs (hereafter, referred to as sample A). This sample has previously been used for a genetic study of leprosy [24, 25]. During the second period (2002–2004), we recruited only patients with leprosy who had experienced T1Rs (hereafter, referred to as sample B).

Leprosy was diagnosed by 2 independent, experienced Vietnamese leprologists, using clinical, bacteriological, and histological data. Clinical forms were defined according to both Ridley-Jopling and WHO classifications. Five patients with indeterminate leprosy (i.e., patients whose leprosy could not be assigned to 1 of the 5 Ridley-Jopling classes previously described) were excluded from the study. As stated by the current WHO guidelines [6], the PB class includes cases of the TT and BT forms of leprosy that have a negative BI and <5 skin lesions. Patients who had all other conditions were classified as having MB leprosy. All patients received multidrug therapy, which consisted of a 6-month course of 2 antibiotics for patients with PB leprosy, and at least 18 months of 3 antibiotics for patients with MB leprosy [26]. During multidrug therapy, and in the absence of T1Rs, monthly clinical examinations were per-

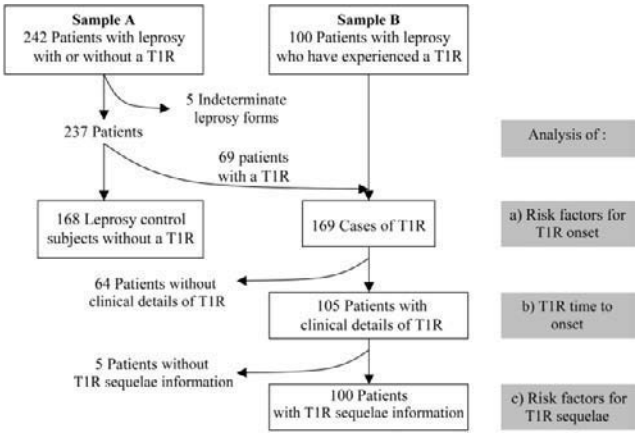

Figure 1. Overview of the sampling procedure and the analysis strategy. T1R, type 1 reaction.

Table 1. Distribution of initial clinical features in the patients with leprosy who have experienced at least 1 type 1 reaction (T1R) (from samples A and B) and control patients with leprosy only (from sample A).

Clinical feature	T1R case patients			Control patients	
	Sample A (n = 69)	Sample B (n = 100)	All (n = 169)	Sample A (n = 168)	All patients (n = 337)
Age at leprosy diagnosis, mean years (95% CI)	19.5 (18.6–20.5)	20.9 (20.1–21.7)	20.3 (19.7–20.9)	17.6 (17.0–18.2)	19.0 (18.6–19.4)
Leprosy subtype					
Ridley-Jopling classification					
TT	7.3	4.2	5.5	26.0	16.0
BT	14.5	12.5	13.3	27.2	20.4
BB	43.5	47.9	46.1	18.5	32.0
BL	33.3	31.3	32.1	18.5	25.1
LL	1.4	4.2	3.0	9.8	6.5
WHO classification					
PB	11.6	14.3	13.2	40.9	27.1
MB	88.4	85.7	86.8	59.1	72.9
No. of skin lesions					
⩽5	41.8	35.4	38.3	65.8	52.6
>5	58.2	64.6	61.7	34.2	47.4
Bacillary index					
Negative	69.1	47.9	56.8	82.6	71.4
Positive	30.9	52.1	43.2	17.4	28.6
Onset of T1R					
Before multidrug therapy	29.0	32.0	30.7	…	…
During multidrug therapy	65.2	59.8	62.1	…	…
After multidrug therapy	5.8	8.2	7.2	…	…

NOTE. Data are % of patients, unless otherwise indicated. BB, mid borderline leprosy; BL, borderline lepromatous leprosy; BT, borderline tuberculoid leprosy; LL, lepromatous leprosy; MB, multibacillary; PB, paucibacillary; TT, tuberculoid leprosy; WHO, World Health Organization.

formed. After cessation of treatment, monthly follow-up examinations were pursued for patients who experienced neurological damage; otherwise, patients were examined once a year.

A T1R was diagnosed if a patient had inflammatory skin lesions (redness or swelling of preexisting or new lesions) and/or acute neuritis (nerve pain, paraesthesia, or sensory or motor deficit), irrespective of general signs. The WHO disability grading [6] was also determined for study patients. Grade 0 corresponds to the absence of all anesthesia, visible deformity, and neurological damage; grade 1, to anesthesia without visible deformity or damage; and grade 2, to visible deformity or damage. Data regarding date of onset and detailed clinical description of the first T1R and occurrence of further T1Rs were collected for all patients in sample B and were available for some patients with T1Rs in sample A. All patients with T1Rs were treated with prednisone for at least 3 months, with the initial dose of 40 mg per day slowly tapered according to fortnightly clinical evaluation.

Methods. First, we conducted a case-control study of the risk factors for T1Rs, where case patients were those from any sample with T1Rs and control subjects were patients in sample A who had leprosy without a T1R. Risk factors for T1Rs were analyzed using univariate and multivariate logistic regression. The explanatory variables were age at diagnosis of leprosy (coded as a quantitative [in years] or categorical [<15, 15–19, 20–24, or ⩾25 years] variable), sex, Ridley-Jopling type of leprosy (coded as a 5-class categorical variable), WHO leprosy form (PB or MB), BI (coded as a categorical [from 0 to 6] or a binary [positive or negative] variable), and number of skin lesions (coded as a quantitative or a binary [⩽5 vs. >5] variable).

We then focused on the group of well-characterized patients who had experienced T1Rs (figure 1) to identify factors influencing (1) the time to T1R onset in months, defined as the time between the diagnosis of leprosy and the onset of the first T1R, and (2) the presence of sequelae after treatment, defined as a disability grade >0 after initiation of steroid treatment for the first T1R. In addition to the explanatory variables quoted above, we analyzed various clinical characteristics of the first T1R: skin lesions, neuritis, sensory or motor deficit, and general signs, each encoded as a binary variable (present or absent). We performed a survival analysis (Cox model) to assess the factors associated with the time to onset of a T1R. The risk of sequelae was analyzed by means of a logistic regression, which tested the same variables plus the time to T1R onset.

Table 2. Logistic regression analysis of the risk factors for the occurrence of type 1 reactions (T1Rs).

Variable	Patients who have experienced a T1R, %	Univariate analysis		Multivariate analysis	
		OR (95% CI)	*P*	OR (95% CI)	*P*
Age at leprosy diagnosis[a]					
<15 years	36.5	1.0	<.001	1.0	.001
⩾15 years	56.5	2.3 (1.4–3.6)		2.4 (1.3–4.1)	
Sex					
Male	47.3	1.0	.059	1.0	.531
Female	59.5	1.6 (1.0–2.7)		1.2 (0.6–2.3)	
Leprosy subtype					
Ridley- Jopling classification					
TT	16.7	1.0	<.001	1.0	<.001
BT	32.8	2.4 (1.0–5.9)		2.0 (0.7–5.4)	
BB	70.4	11.9 (5.2–27.1)		7.3 (2.6–20.3)	
BL	63.1	8.5 (3.6–19.8)		2.4 (0.7–7.4)	
LL	26.3	1.8 (0.5–6.2)		0.2 (0.0–1.1)	
WHO classification					
PB	23.9	1.0	<.001	1.0	.844
MB	59.7	4.7 (2.7–8.1)		0.9 (0.3–2.9)	
Bacillary index					
Negative	40.9	1.0	<.001	1.0	.002
Positive	71.4	3.6 (2.2–6.0)		3.2 (1.5–6.6)	
No. of skin lesions					
⩽5	34.2	1.0	<.001	1.0	.021
>5	61.7	3.1 (2.0–4.9)		2.2 (1.1–4.3)	

NOTE. Data were the result of analysis of 169 patients with leprosy who had experienced at least 1 T1R and 168 control subjects. BB, mid borderline leprosy; BL, borderline lepromatous leprosy; BT, borderline tuberculoid leprosy; LL, lepromatous leprosy; MB, multibacillary leprosy; PB, paucibacillary leprosy; TT, tuberculoid leprosy; WHO, World Health Organization.

[a] Binary encoding is presented for a simpler interpretation of ORs, but the effect was also significant when using raw quantitative values.

All statistical analyses were performed using SAS software, version 8 (SAS Institute), using the LOGISTIC and PHREG procedures.

RESULTS

Sample description. Figure 1 presents an overview of the samples that were used in the different analyses. A total of 337 patients with leprosy were included: 237 from sample A and 100 from sample B (see table 1 for detailed clinical features). The dates of leprosy diagnosis were from 1991 to 2000 for sample A and from 1991 to 2004 for sample B. The population had a male:female ratio of 3.3, and the mean age at diagnosis was 19 years (range, 2–46 years). Seventy-three percent of patients had MB forms of leprosy.

In sample A, 69 (29.1%) of the 237 patients experienced at least 1 T1R. This sample was constituted irrespective of a patient's T1R status; therefore, this estimate can be interpreted as the prevalence of T1Rs among patients with leprosy who are treated at the Ho Chi Minh City Dermatology Hospital. The prevalence of T1Rs by Ridley-Jopling leprosy class was TT, 10.0%; BT, 18.2%; BB, 49.2%; BL, 43.4%; and LL, 6.7%. The prevalence of T1Rs among patients with PB and MB leprosy was 10.3% and 38.9%, respectively.

Sample B consisted of 100 patients who had T1Rs. Their main baseline clinical features did not differ significantly from those of the 69 patients with T1Rs in sample A (table 1), except for a higher BI ($P = .03$). Of the 169 total patients with T1Rs (in sample A and sample B), 30.7% experienced their first T1R at the time of leprosy diagnosis, 61.1% during multidrug therapy, and 7.2% after cessation of treatment; these proportions were similar among the 2 samples (table 1).

Risk factors for T1Rs. We compared the 169 case patients who had experienced T1Rs (69 from sample A and 100 from sample B) with the 168 leprosy control subjects (table 2). Univariate analysis identified several risk factors for T1Rs. The most significant was leprosy subtype—that is, borderline classes (figure 2*A*) and MB form of leprosy were associated with a higher risk of T1Rs. Two other initial characteristics of leprosy dis-

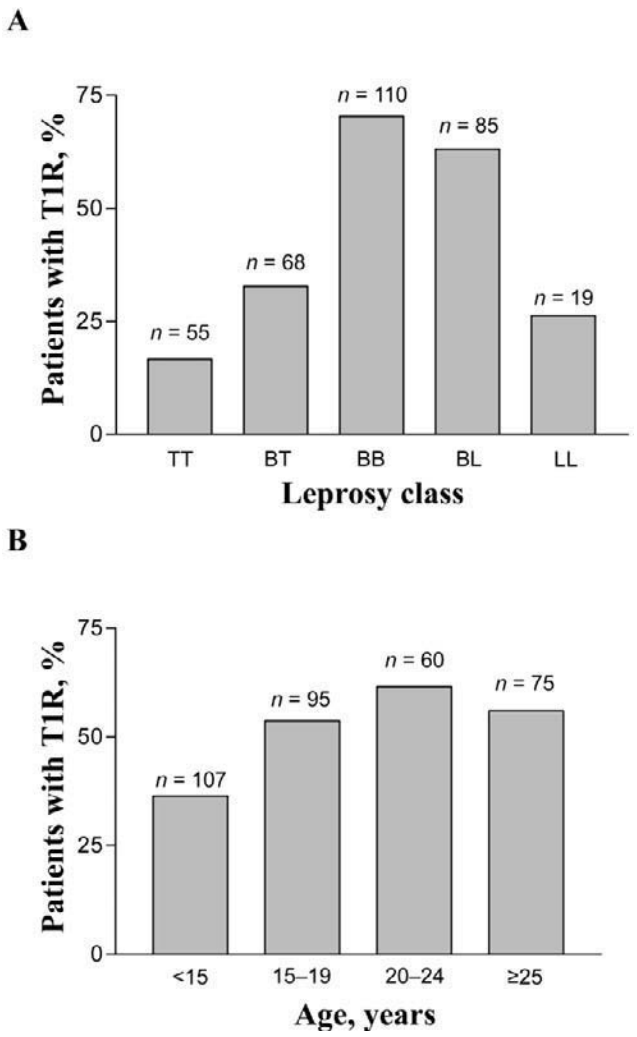

Figure 2. Proportion of patients with leprosy who had at least 1 type 1 reaction (T1R) in the entire sample (337 patients), according to Ridley-Jopling leprosy classes *(A)* and age classes *(B)*. BB, mid borderline leprosy; BL, borderline lepromatous leprosy; BT, borderline tuberculoid leprosy; LL, lepromatous leprosy; TT, tuberculoid leprosy.

ease—a large number of skin lesions and a positive BI—were also significant. With BI as a categorical variable (7 classes), there was no statistical difference of risk for T1R occurrence between grades 1–6, so binary encoding (0 or ⩾1) was used for further analyses. The BI in patients who had experienced T1Rs in sample A was lower than that in patients in sample B; however, it is noteworthy that a positive BI remained significantly associated with T1R occurrence in patients in sample A. Age at leprosy diagnosis was also a significant risk factor, whether coded as a quantitative or a categorical variable. Patients <15 years of age were less prone to developing T1Rs than were older patients (figure 2*B*). In a multivariate analysis, 4 covariates remained highly significant: Ridley-Jopling leprosy classes (OR, 6.3 [95% CI, 2.9–13.7] for the borderline leprosy groups vs. the polar forms of leprosy), BI (OR, 3.2 [95% CI, 1.5–6.6] for positive vs. negative value), number of skin lesions (OR, 2.2 [95% CI, 1.1–4.3] for >5 vs. ⩽5 lesions) and age (OR, 2.4 [95% CI, 1.3–4.4] for patients aged ⩾15 years vs. <15 years). As expected, the effect of WHO classes was not significant after adjustment for Ridley-Jopling leprosy forms.

Analysis of the time to onset of T1R. Detailed characteristics of the patient's first T1R were available for all patients in sample B and for 5 patients in sample A (a total of 105 patients; table 3). Overall, pure skin, pure neurological, and mixed skin-neurological involvements were present in 24 patients (22.9%), 12 patients (11.4%), and 69 patients (65.7%), respectively. The distribution of the time to T1R onset is detailed in figure 3*A*. Briefly, 32 T1Rs (30.8%) were already present at leprosy diagnosis, and an additional 58 T1Rs (54.8%) occurred within the first 12 months of follow-up. The latest T1R occurred 51 months after the diagnosis of leprosy. No risk factor was identified as influencing the time to onset and, in particular, no association with leprosy subtype was detected (figure 3*B*). However, we found that T1Rs with neuritis occurred much earlier than pure skin T1Rs ($P = .001$; figure 3*C*).

Risk factors for T1R sequelae. Reliable information about sequelae was available for 100 (95.2%) of the 105 patients with T1R. After receipt of corticosteroid treatment for the first T1R, 47 patients (45.2%) had a disability grade >0. Three variables

Table 3. Detailed clinical features of the first episode of a type 1 reaction (T1R) in 105 patients.

Clinical features	Percentage of patients
Neuritis	
At least 1 feature	77.1
Pain	77.1
Sensory or motor deficit	41.0
Skin lesions	
At least 1 feature	88.6
Thickness or redness	82.9
New skin lesions	19.2
General signs	
At least 1 feature	57.1
Edema	21.0
Discomfort	42.9
Fever	34.3
Disability grade after treatment of T1R	
0	54.8
1	20.4
2	24.8
No. of T1R episodes	
1	69.5
2	23.9
3	4.8
4	0.9
5	0.9

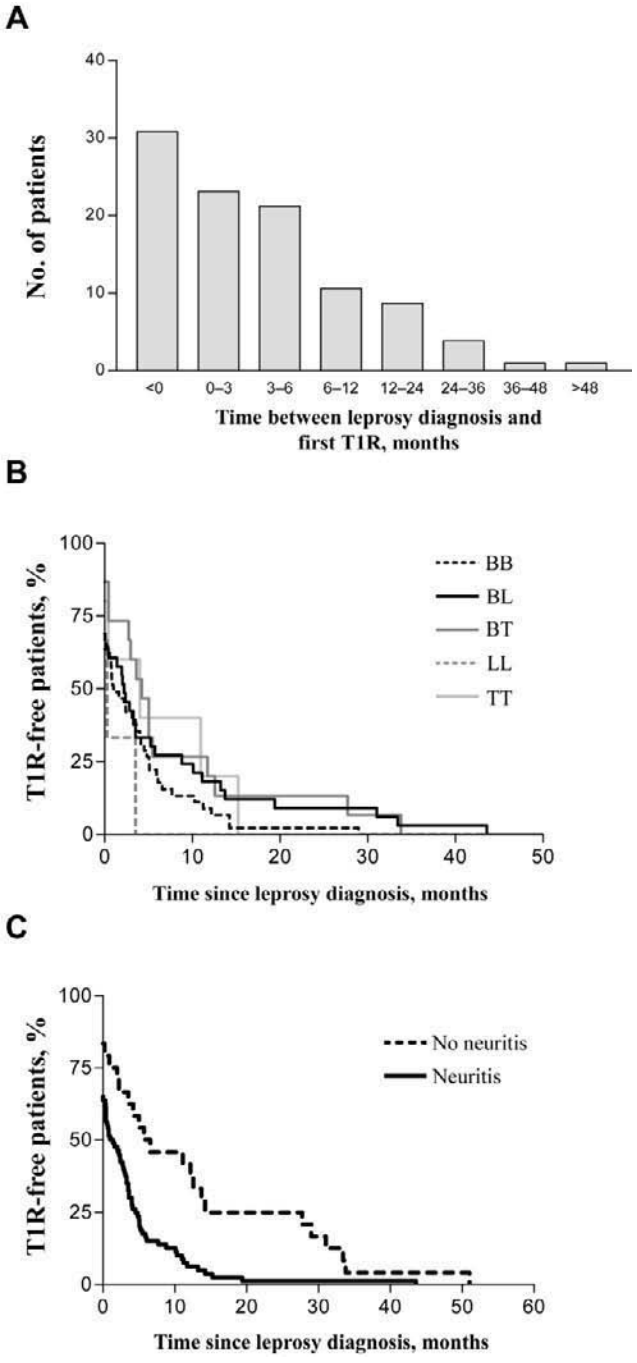

Figure 3. Time to onset of the first type 1 reaction (T1R) in 105 patients with at least 1 T1R. Distribution of patients according to the time between the diagnosis of leprosy and the onset of the first T1R *(A)*. Survival curves of the first T1R onset, as estimated by the Kaplan-Meier method, according to the Ridley-Jopling leprosy class *(B)* and the presence or absence of neurological involvement (neuritis) *(C)*. No significant difference was observed in the T1R time to onset according to the 5 Ridley-Jopling leprosy classes, whereas time to onset was significantly shorter ($P = .001$) in patients with neuritis compared with others. BB, mid borderline leprosy; BL, borderline lepromatous leprosy; BT, borderline tuberculoid leprosy; LL, lepromatous leprosy; TT, tuberculoid leprosy.

were significant risk factors for T1R sequelae: presence of sensory or motor deficit at onset of T1R, >5 skin lesions, and age at leprosy diagnosis. Interestingly, age was significant, whether coded as a quantitative or a categorical variable (threshold, 20 years; figure 4). In multivariate analysis, the only significant risk factors for sequelae were sensory or motor deficit (OR, 5.4 [95% CI, 1.9–16.0]) and age (OR, 4.4 [95% CI, 1.7–11.6] for patients ⩾20 years vs. <20 years).

DISCUSSION

In this hospital-based study of Vietnamese leprosy patients, using a broad definition of T1Rs that includes pure skin and pure neural inflammation (as is widely applied in the literature [7, 19]), the overall prevalence of T1Rs was 29%. It is unlikely that we underestimated the number of cases of T1Rs, because late-onset T1Rs occur mostly within 3 years after the diagnosis of leprosy and the median follow-up of the study cohort was 5 years [8, 10, 12, 23]. One of the difficulties with comparing the prevalences of T1Rs in different studies is that authors define a T1R differently (e.g., excluding or including pure neuritis) and use different methods of diagnosis (hospital based or outpatient based and active case finding or self reporting). Moreover, geographic and ethnic variation among the proportions of leprosy subtypes also contributes to significant heterogeneity in reported prevalences, because T1Rs occur predominantly in patients with borderline leprosy. Consistent with observations in previous studies [10–12], the T1R prevalence was highest among patients with the BB and BL types of leprosy in this sample of Vietnamese case patients with leprosy (prevalence of 49% and 43%, respectively). Importantly, multivariate analysis revealed that borderline forms of leprosy are independent risk factors for T1Rs, as is a positive BI at leprosy diagnosis. Finally, the number of skin lesions at diagnosis was also an independent risk factor for T1R in our sample, which is con-

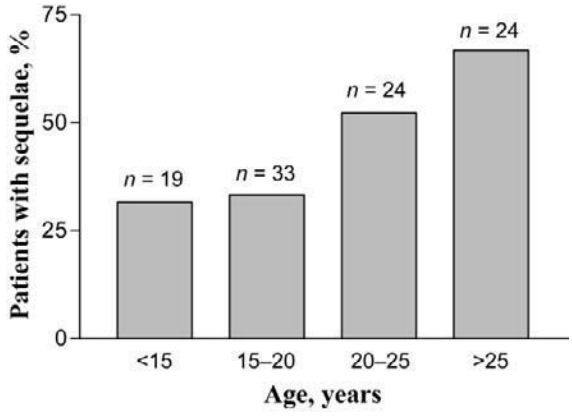

Figure 4. Proportion of sequelae (disability grade >0 after steroid treatment) after the first type 1 reaction (T1R) episode, among 100 patients, according to age class.

sistent with the documented impact of the extent of clinical disease on the risk of a T1R [9–12].

The major original finding of our study is that age is an independent risk factor for the occurrence of T1Rs. Of note, because an inclusion criterion of our study was that both parents of the subject were alive, children were overrepresented in our sample, which clearly contrasted with previous studies [12, 23]. The reason children are at a lower risk for T1Rs is unknown. A previous study found a 10-times greater prevalence of T1Rs in patients with leprosy who self reported their condition than in patients with actively detected leprosy, with a lower proportion of children <15 years among self-reporting than among actively detected patients (10% vs. 25%) [27]. This observation was attributed to a more advanced state of disease in self-reporting patients (a population that consisted mostly of adults) [27], and may partially explain our finding. Similarly, patients with a household leprosy contact are likely to be diagnosed earlier; the lower risk of T1Rs that we observed in children could result from a higher frequency of household contacts. Indeed, in our study, the proportion of individuals <15 years old was 28% among patients with healthy parents (239 patients), compared with 39.8% among patients with at least 1 parent with leprosy (98 patients). However, stratified analysis showed that patients with T1Rs were significantly older in both subsamples ($P = .02$ and $P = .05$, respectively), which demonstrates that age effect on the risk for T1Rs is independent of the presence of parental contact. Alternatively, 2 specific features of a child's immune system may contribute to T1R onset. First, a strong Th2 bias has been observed in the immune response to infections in human infants [28] and more extensively documented in neonatal mice [29]. Because T1Rs are associated with a strong Th1 polarization, this might explain the lower frequency of T1Rs in young children. Second, the T cell repertoire is progressively constituted throughout childhood. Moreover, it has been suggested that T1Rs can result from antigenic cross-reaction secondary to non–*M. leprae* mycobacterial infection, such as tuberculosis [30]. It is, therefore, plausible that adults, because of their broader memory T cell repertoire, show more frequent T1Rs that are triggered by cross-reaction to *M. leprae* antigens following sensitization by non–*M. leprae* mycobacterial infection.

The distribution of times to T1R onset in this sample of Vietnamese patients was consistent with those reported previously [8, 10, 12, 21]. Over 30% of T1Rs were detected at diagnosis of leprosy, 55% were observed within the 12 months following diagnosis, and <15% were detected after the first year of follow-up. The only factor significantly associated with a short time to onset in our study was T1R neuritis; this is in contrast with the findings of Lockwood et al. [21], who observed more frequent neurological involvement in late-onset reactions. T1Rs were frequently associated with residual disabilities, even after administration of an appropriate steroid treatment [13, 19]; 42% of our patients experienced sequelae, defined as a high disability grade after the first T1R. Although we could not differentiate the consequences of leprosy from those of T1Rs, these sequelae are likely to result mostly from the reaction, because their most significant risk factor was sensory or motor deficit at T1R onset. Similarly, an Indian study [21] reported better improvements of skin lesions (93%) than nerve impairment (51%) after steroid treatment for T1Rs. We also show that the risk of sequelae is dependent on age at leprosy diagnosis, with patients aged >20 years being more likely than younger patients to experience sequelae. Overall, our study strongly suggests that young patients have significant protection against both the occurrence and the severity of T1Rs.

T1Rs are a major cause of nerve impairment in cases of leprosy, yet their physiopathology is poorly understood. Epidemiological studies help to dissect the pathological process by identifying population risk factors. Here, we report that borderline forms of leprosy, positive BI, and leprosy with extensive skin involvement are independent risk factors for T1Rs. In addition, we clearly show that age is an important risk factor for the onset and the prognosis of T1Rs. Finally, the heterogeneity of risk for T1Rs among individuals and ethnic groups strongly suggests the involvement of host genetic factors in the pathogenesis of these reactions, as it is the case for the leprosy disease itself [31]. We are currently conducting a large genetic epidemiology study to determine the genetic basis of T1R onset in patients with leprosy. Timely identification of patients with leprosy who are at increased risk of T1Rs will allow for the targeting of more intense preventive care to such patients.

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Potential conflicts of interest. All authors: no conflicts.

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