Pubertal development of transfusion-dependent thalassemia patients in the era of oral chelation with deferasirox: results from the French registry

Over the last decades, advances in transfusion regimen, chelation therapy and iron overload monitoring have allowed a steady increase in life expectancy of patients with transfusion-dependent thalassemia (TDT), mainly related to a decrease in cardiac mortality.[1,2] However, endocrinopathies remain the most frequent and early complications of iron overload in TDT patients, the first being hypogonadism with a prevalence ranging from 30 to 60% in numerous registries and cohorts.[3-5] Early diagnosis and treatment are essential to achieve normal puberty, target height, and reduce the risk of long-term infertility and sexual dysfunction. It has been established that well-managed chelation therapy and its early initiation, allowing good control of iron overload, reduce the risk of hypogonadism.[6,7] However, definitions of pubertal disorders and hypogonadism vary according to studies, and data from the literature regarding pubertal development are often incomplete.

The French National Thalassemia Registry (NaThalY) has recently initiated a study on the health status of TDT children aged <15 years, mostly (80%) under deferasirox (DFX) therapy, reporting an excellent probability of survival (98.3%) and a very low rate of iron-related complications.[8] In the context of the global improvement in endocrinopathies already described under DFX,[9] here we report the remaining pubertal disorders and hypogonadism in TDT adolescents and young adults included in the French Thalassemia Registry who received oral chelation with DFX before puberty onset. This study respects the French ethical rules. The French registry was approved by the Comission Nationale de l'Informatique et des Libertés (CNIL) (declaration N. 903064V1, authorization N. 04-1396).

A total of 50 patients, treated in 24 registry-participating centers, accumulated at least three years of DFX therapy before puberty in their history of chelation therapy and met the inclusion criteria of this study (Figure 1). Their median age at last visit was 20 years for girls (N=25, range 14-24) and 18 years for boys (N=25, range 14-24). Regular transfusions and chelation therapy were initiated early, at 1.3 years old (range 0.3-4) and 3 years old (range 1-6), respectively. The median duration of DFX chelation before 13 years in girls and 14 years in boys was seven years (range 3-12).

All 50 patients were evaluable for pubertal delay, defined as lack of pubertal onset by 13 years in girls and 14 years in boys. All had spontaneous puberty onset, at a median age of 12.5 years in girls (range 10.5-14) and 13.5 years in boys (range 12.5-15). Eight patients (16%) experienced delayed puberty, mostly (7/8) simple pubertal delay, with a delay ranging from 6 to 12 months (Table 2). Among the 7 patients with simple pubertal delay, 5 were boys.

Only one patient, suffering from a pubertal delay, presented with primary amenorrhea out of the 24 girls who had either menstruated or who were >15 years old (4.2%). Median age at first menstruation was 13.5 years (range 12-17). Two girls had their first menstruation delayed, at 16 and 17 years old, both after a simple pubertal delay.

Twenty-three patients were assessable for secondary amenorrhea (menstruated girls). Three developed secondary amenorrhea (13%) 2, 3, and 7 years after their menarche. Mean follow-up duration after menarche for the 20 other girls without secondary amenorrhea was 6.3 years.

The 4 patients with primary or secondary amenorrhea had hypogonadism with low sexual hormone levels (estradiol <25 pg/mL). Three showed hypogonadotropic hypogonadism (HH) (*Online Supplementary Table S1)*. Despite existing HH,

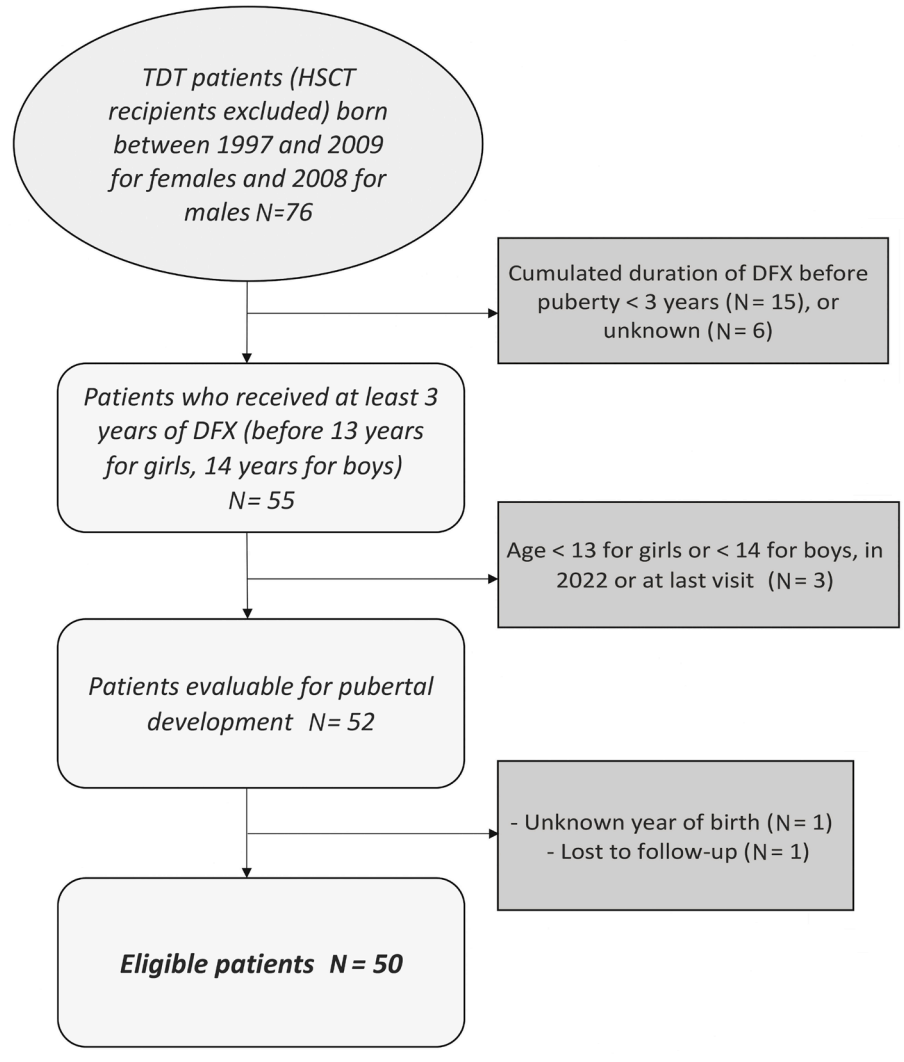

Figure 1. Study population. DFX: deferasirox; HSCT: hematopoietic stem cell transplantation; TDT: transfusion-dependent thalassemia.

Table 1. Clinico-biological characteristics of study population.

Characteristic	Included patients N=50	Normal puberty N=39	Pubertal development disorders or hypogonadism, N=11
Sex, N (%)			
Boys	25 (50)	20 (51.3)	5 (45.5)
Girls	25 (50)	19 (48.7)	6 (54.5)
Age at evaluation in years, median (IQR)	18.5 (17-21.8)	18 (16.5-22)	20 (17-21)
Range	14-24	14-24	16-23
Genotype, N (%)			
beta0 / beta0	38 (76)	28 (71.8)	10 (90.9)
beta0/ beta+	10 (20)	9 (23.1)	1 (9.1)
NA	2 (4)	2 (5.1)	0 (0)
Place of birth, N (%)			
France	39 (78)	29 (74.4)	10 (90.9)
Outside France	11 (22)	10 (25.6)	1 (9.1)
Age at care in France in years, median (IQR)	4 (2-5.5)	4 (2-6)	2
Range	0-15	0-15	-
Age at first transfusion in years, median (IQR)	1.3 (0.5-2.3)	1.3 (0.6-2)	1.2 (0.4-2.4)
Range	0.2-4	0.3-4	0.3-4
NA, N (%)	6 (12)	4 (10.3)	2 (18.2)
Age at chelation onset in years, median (IQR)	3 2-4	3 2-4	3 2-4
Range	1-6	1-6	1-6
NA, N (%)	2 4%	2 5.1%	0 0%
First chelator prescribed, N (%)			
DFX	23 (46)	18 (46.2)	5 (45.5)
DFO	26 (52)	20 (51.3)	6 (54.5)
DFP	1 (2)	1 (2.6)	0 (0)
Chelator at 13 (girls) or 14 (boys) years, N (%)			
DFX	43 (86)	33 (84.6)	10 (90.9)
DFO	1 (2)	0 (0)	1 (9.1)
DFP	4 (8)	4 (10.3)	0 (0)
Bi-therapy	2 (4)	2 (5.1)	0 (0)
DFX accumulated duration before puberty in years, median (IQR)	7 (5-9)	7 (5-9)	6 (5-7.5)
Range	3-12	3-12	3-12
NA, N (%)	1 (2)	1 (2.6)	0 (0)
Other endocrine disorder, N (%)			
GH deficiency	6 (12)	4 (10.3)	2 (18.2)
Diabetes	1 (2)	0 (0)	1 (9.1)
Central hypothyroidism	1 (2)	1 (2.6)	0 (0)
Ferritin, microg/L,** median (IQR)			
Mean at 10 years old	1,092 (700-1,859)	1,092 (643-1,859)	1,158 (848-2,045)
NA, N (%)	2 (4)	1 (2.6)	1 (9.1)
Mean between 10 years old and puberty	978 (624-1,409)	983 (670-1,409)	950 (399-2,084)
NA, N (%)	1 (2)	1 (2.6)	0 (0)
History of ferritin >2,500 microg/L twice or more*, N (%)	18 (36)	13 (33.3)	5 (45.5)
Liver iron concentration LIC, mg/g dw,** median (IQR)			
Mean at 10 years old	6.3 (3.9-12.2)	6.2 (3.8-12.2)	6.9 (5-11.7)
ND, N (%)	10 (20)	9 (23.1)	1 (9.1)
NA, N (%)	2 (4)	1 (2.6)	1 (9.1)
Mean between 10 years old and puberty	4.9 (2.9-9.7)	4.8 (3-9.7)	6.2 (2.5-11.9)
ND, N (%)	6 (12)	4 (10.3)	2 (18.2)
NA, N (%)	2 (4)	2 (5.1)	0 (0)
History of LIC >15 mg/g, N (%)	12 (24)	7 (17.9)	5 (45.5)
NA, N (%)	3 (6)	3 (7.7)	0 (0)

IQR: interquartile range; DFO: deferoxamine; DFP: deferiprone; DFX: deferasirox; dw: dry weight; GH: growth hormone; LIC: liver iron concentration; NA: not available; ND: not done. *At least 12 months apart. **No statistically significant difference was noted in clinical/biological characteristics of patients with and without disorders.

one patient experienced a spontaneous pregnancy, the only one reported in the cohort. The fourth female had hypogonadism of mixed origin, with a suspected premature ovarian failure (low anti-Mullerian hormone: 1.14 pmol/L) and only moderate elevation of follicle-stimulating hormone (FSH) (15 UI/L), probably due to pituitary overload. No paternity was reported.

No puberty abnormalities other than simple pubertal delay were noted in boys. Completion of puberty for the 18 male patients aged >17 years was clinically assessed (Table 2), biological data not being routinely collected in the registry. Finally, a total of 11 patients (22%) experienced simple delayed puberty (N=7) or hypogonadism (N=4). No significant difference was noted between these patients and the rest of the cohort concerning the age at first transfusion, the age at chelation onset or the cumulative duration of DFX before puberty (Table 1). Among these 11 patients, 7 had a history of severe iron overload before puberty (serum ferritin levels >2,500 µg/L twice at least 12 months apart or liver iron content >15 mg/g dry weight) compared with 13/39 patients who did not experience pubertal development disorders or hypogonadism (*P*=0.1). All 4 patients with hypogonadism already had a history of severe iron overload before the onset of puberty.

Table 2. Characteristics of pubertal development according to gender.

Characteristic	Total, N=50	Girls, N=25	Boys, N=25
Age at evaluation in years, median (IQR) Range	18.5 (17-21.8) 14-24	20 (17-22) 14-24	18 (16-20) 14-24
Age at pubertal onset in years, median (IQR) Range	13 (12.5-13.5) 10-15	12.5 (11.5-12.5) 10.5-14	13.5 (13.5-13.5) 12.5-15
Age at menarche in years, median (IQR) Range NE (Non-menstruating <15 years), N (%)	- - -	13.5 (12.5-14) 12-17 1 (4)	- - -
Age at end of puberty in years, median (IQR) Evaluated, N (%) NE (<17 years at assessment), N (%) NA, N (%)	17 (16-17) 37 (74) 11 (22) 2 (4)	16 (16-17) 20 (80) 4 (16) 1 (4)	17 (17-18) 17 (68) 7 (28) 1 (4)
Disorders of pubertal development°, N (%) Pubertal delay Including simple pubertal delay Primary amenorrhea* Secondary amenorrhea** Arrested puberty	11 (22) 8 (16) 7 (14) - - 1 (2)	6 (24) 3 (12) 2 (8) 1 (4.2) 3 (13) 1 (4)	5 (20) 5 (20) 5 (20) - - 0 (0)
Hormonal replacement therapy, N (%)	2 (4)	2 (8)	0 (0)
Height, SD°°, median (IQR) At 10 years NA, N (%) Pre-pubertal height NA, N (%) Final height† Evaluated, N (%) NE (< 17 years at assessment), N (%) NA, N (%)	 -0.7 (-1.3 to 0) 4 (8) -1.2 (-1.7 to -0.3) 3 (10) -0.7† (-1.2 to 0) 35 (70) 11 (22) 4 (8)	 -0.8 (-1.5 to -0.1) 2 (8) -1.2 (-1.7 to -0.2) 1 (4) -0.3 (-1.1 to 0) 19 (76) 4 (16) 2 (8)	 -0.7 (-1.2 to 0) 2 (8) -1.2 (-1.8 to 0.8) 2 (8) -0.8 (-1.2 to -0.5) 16 (64) 7 (28) 2 (8)
Pubertal spurt in cm, median (IQR) Evaluated, N (%) NE (<17 years at assessment), N (%) NA, N (%)	20.5 (17-24.5) 34 (68) 11 (22) 5 (10)	18 (16.5-22) 19 (76) 4 (16) 2 (8)	22 (20.5-26) 15 (60) 7 (28) 3 (12)

IQR: interquartile range; NA: not available; NE: not evaluable; SD: standard deviation. *Evaluable patients N=24. **Evaluable patients N=23. °Pubertal delay: lack of testicular development (testis volume <4 mL) in boys aged 14 years (Tanner stage <G2) or absence of thelarche in 13-year old girls (Tanner stage <S2). Simple pubertal delay: puberty with delayed onset but then proceeding normally, without the need for any treatment. Arrested puberty: failure to continue pubertal progression over a period of two years after spontaneous onset of puberty, or a delay between thelarche and menarche of four years or more. End of puberty: Tanner stage 5 and growth completed. °°Pre-pubertal height: last height available in the year of puberty onset. Final height: height reached at the end of puberty, no difference between two visits at least 12 months apart. Pubertal spurt: final height - pre-pubertal height. Height in cm were converted to SD according to French Growth Charts. †As patients originated from various countries, heights were also converted to SD according to the WHO growth chart; median final height was -0.6 SD (-0.2 SD in girls, -0.9 SD in boys).

Although the age at onset of puberty and at first menstruation remained delayed in TDT patients compared with the general French population (i.e., 10.5 years in girls and 12 in boys, 12 years for menarche),[10] the frequency of delayed puberty in this study was lower than previously reported under well-conducted deferoxamine (DFO) treatment,[5,7,11] and rarely evolved into hypogonadism.

Height was moderately reduced at the age of 10 years (-0.8 Standard Deviation [SD] in girls, -0.7 SD in boys), then going down to -1.2 SD for both genders reflecting pre-pubertal inflection. Most patients then experienced pubertal growth spurt, with a median of 18 cm in girls and 22 cm in boys. Final height, reached in 35/50 patients, was only moderately reduced (-0.7 SD), with a median height of 161 cm in girls (-0.3 SD) and 168.5 cm in boys (-0.8 SD) (*Online Supplementary Figure S1*). Patients with impaired pubertal development or hypogonadism had a median final height of -0.3 SD (Table 2). Six patients (4 boys, 2 girls) had growth hormone (GH) deficiency, of whom 3 had a history of severe iron overload before puberty. Age at GH treatment onset ranged from 12 to 15 years. There was no difference in final height when GH-treated patients were excluded. Despite pubertal spurts lower than those reported for the general population (25 cm in girls and 28 cm in boys),[10] final heights have improved in comparison with those previously reported under DFO in the French registry (-1.2 SD).[4] Another study found that final height was -1.9 SD in patients exclusively chelated by DFO, compared with -1.2 SD in patients who had been chelated with DFX for at least six years.[5] This difference could be due in part to the well-documented direct deleterious effect of DFO on growth in young children.

Regarding other endocrine disorders, one patient developed central hypothyroidism during adolescence and one patient had type 1 diabetes, which was not related to iron overload as it occurred early in childhood (7 years old) with evidence of autoantibodies. No cardiac or hepatic disorders were reported. One patient with severe iron overload and HH died at 17 years from septic shock; this was the only death reported in the cohort.

Deferasirox was first marketed in the European Union in 2007 and since then has been the most widely prescribed iron chelator for TDT patients in Europe and the United States. This oral chelation therapy has been associated with decreased frequency of endocrine complications including hypogonadism in adult patients.[12] Scarce published data (few patients studied) document the frequency of pubertal delay in TDT adolescents receiving DFX. An American study found a rate of pubertal disorders (both simple delay and hypogonadism) in 4 out of 15 adolescents.[13] In another study, incidence of simple pubertal delay was evaluated at 15%, i.e., 3 out of the 20 TDT patients who had been pre-pubertal at the start of the study and had received at least three consecutive years of DFX.[9]

It remains difficult to distinguish between an improved global control of iron overload and a possible specific effect of DFX on the prevention of pubertal disorders secondary to iron overload. Indeed, the once-daily oral administration of DFX improved adherence with the daily lifelong chelation therapy prescribed.[14] Additionally, DFX, with its prolonged half-life and permanent blood exposure could allow better pituitary protection, secondary to continuous chelation of non-transferrin-bound iron.

To our knowledge, our study is the first to provide detailed information on puberty development and to document its improvement in a large cohort of 50 adolescents treated with DFX. This is a retrospective multicenter registry study and data concerning family history of growth and puberty or adherence to chelation are missing, and there is no systematic uniform endocrinological follow-up of puberty. Thus, while in girls, objective events such as the occurrence of the first menstruation and the regularity of cycles provide a simple means to monitor puberty, assessment is more difficult in boys. This less accurate monitoring means that the rate of arrested puberty or early hypogonadism in boys is probably underestimated. Given the impact of pubertal and growth disorders on patients' quality of life and on future fertility, the systematic integration of an endocrinologist in the healthcare team of TDT children and adolescents is currently recommended in national and international guidelines. Additionally, the patients studied are still young and cannot yet be assessed for the occurrence of hypogonadism in adulthood, the frequency of which increases with age.[4,7,15] It is, therefore, important in the near future to accurately evaluate the effect of long-term DFX chelation therapy on the prevention of hypogonadism in TDT young adults.

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Contributions

MVB and AB performed the research. MVB, JV and IT wrote the manuscript. SS and IT supervised the study. All authors critically revised the manuscript and approved the final version for publication.

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Data-sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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