Clinical history and high prevalence of gonadal tumor in 14 patients with 46 XY pure gonadal dysgenesis

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Background: Pure gonadal dysgenesis 46 XY, or Swyer syndrom, is a rare form of sexual differentiation disorder, with normal feminine external genital organs, mullerian organs, no functional gonad and 46 XY karyotype without mosaic. Few series of patients with pure gonadal dysgenesis 46 XY are described in literature data. Prevalence tumor in this population is estimated about 20-40% (Michala, BJOG 2008).

Objective: This study describes the diagnosis circumstances, clinical, biological and radiological presentation, and genetic aetiology of 14 patients with a 46 XY pure gonadal dysgenesis. It is a retrospective descriptive multicenter study from Necker Hospital (Paris) and Lille university hospitals.

Main results:
The patients were diagnosed between prenatal period and 21 years, the median age of diagnosis was 16.
9 of the 14 patients had primary amenorrhea, leading to the late diagnosis. 6 of the 9 patients aged 10 years and older had already breast development, without any functional gonad; all of these patients had gonadal tumor, gonadoblastoma and/or dysgerminoma. One patient was diagnosed because of abdominal pain due to a tumoral syndrome.

Eight of the 13 operated patients (61 %) had a gonadal tumor (2 gonadoblastoma and 6 dysgerminoma). Six of the 8 gonadal tumor (75%) were malignant, one of them without preexisting gonadoblastoma. All of those patients were asymptomatic. Bilateral gonadoblastoma was diagnosed for 4 patients. Two patients had a late stage dysgerminoma, so they received chemotherapy (n°6-8). The median age of tumor's diagnosis was 15 years, and the youngest patient was 2 years 11 months old.

Mutation or deletion was found for 5/10 patients, 3/10 (30%) in the coding sequence of the SRY gene : 2 mutations and 1 deletion. 1 patient had a heterozygote mutation in the SF1 gene. 1 had a deletion in the short arm of chromosome 9 including DMRT1 and DMRT2 genes.

N°	Diagnosis circumstances		Pubertal stage		Histology			Genetical aetiology
			Age	Tanner	Age	Tumor	Type	
1	Prenatal	prenatal karyotype			2 y 11 m	Yes (left)	Gb L	
2	Prenatal	prenatal karyotype	10 y 8 m	S1P3		No		
3	Neonatal	polymalformatif sd	14 y 2 m	S1P3		No		
4	17 months	polymalformatif sd			6 y 4 m	Yes	Gb L Dg + Gb R	Deletion short arm chr 9
5	8 years 6 m	abdominal pain			6 y 8 m 9 y 6 m	Yes	Gb L Gb R	Mutation SRY gene
6	15 years	primary amenorrhea + pelvien tumor	14 y 7 m	S5P5A5	14 y 4 m	Yes (left)	Dg stage 3 + Gb L	
7	16 years	primary amenorrhea	17 y 9 m	S4P5	18 y 7 m	Yes (right)	Dg pur R	Deletion SRY gene
8	16 years	primary amenorrhea	16 y 3 m	S3A3P4	17 y 6 m	Yes	Dg + Gb L Gb R	
9	16 y 10 m	primary amenorrhea	16 y 10 m	S4P5A5	17 y 9 m	Yes	Gb L Dg + Gb R	
10	17 years	impuberisme + primary amenorrhea	16 y 4 m	S1A2P5		No		Mutation SF1 gene
11	17 years	primary amenorrhea	17 y 8 m	S2P3A3	21 y	Yes	Gb L Gb + Dg R	
12	17 y 1 m	impuberisme + primary amenorrhea	17 y	S1P2		No		
13	18 years	primary amenorrhea	18 y 7 m	S1P2A3		No		
14	21 years	primary amenorrhea	21 y 4 m	S3P5A4				Mutation SRY gene

Gb : gonadoblastoma, Dg : dysgerminoma, L : left, R : right.

Conclusion

Sixty-one percent of the operated patients had gonadal tumor (gonadoblastoma or dysgerminoma), which is more than literature data. Breast development, even normal appearance, is often due to a tumoral hormonal secretion.
We should not delay ablation of the gonads in patients with 46 XY pure gonadal dysgenesis.
All primary amenorrhea have to be investigated, and a caryotype must be done, even if it seems isolated with a late Tanner stage.

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