Genital tract function in men with Noonan syndrome

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Abstract
In order to study the pattern of male fertility in Noonan syndrome, and its potential implications for genetic counselling, the genital tract function was studied in 11 adult males with Noonan syndrome. Bilateral testicular maldevelopment occurred in six. The mean testicular volume was 21 (SD 4) ml. The stretched flaccid penile length was 11.4 (SD 1.2) cm. Puberty was delayed in three. Four of the men had fathered children. The LH and testosterone levels were essentially normal in all men, while the FSH levels were grossly raised in the group with testicular maldevelopment, with the exception of one man. Semen samples were obtained from five men, and azoospermia or oligozoospermia was present in four of them. Sexual function is not affected in men with Noonan syndrome, but the onset of sexual activity was delayed in men with late onset of puberty. Bilateral testicular maldevelopment appears to be the main factor contributing to impairment of fertility in men with Noonan syndrome.

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affected include the cardiovascular, eye, and skeleton in addition to disorders of growth and development. Coagulation abnormalities have been recently shown in a large cohort of patients.³ Short stature is a common feature, although the nature of the growth failure is unknown, and up to three quarters of boys with this syndrome may have undescended testes.

It has been known that delayed puberty may occur in both sexes, but fertility does not seem to be affected in females. Previous studies in males have reported a variable pattern of pubertal development,⁴⁻⁶ but little is known about genital tract function.⁷ The aim of this paper was to study the genital tract function in men with Noonan syndrome.

Methods
In a previous study at St George's Hospital,⁸ 151 persons (83 males and 68 females) were diagnosed as having Noonan syndrome. The widest possible ascertainment was achieved through referrals from consultant paediatricians, paediatric cardiologists, and clinical geneticists in the UK, in addition to referrals from the Noonan Syndrome Society.

For the purpose of this work, ethical approval was given to recruit men 18 years or older who are of normal intelligence from the male cohort of the above mentioned study.⁸

Eleven of the 17 men who were approached by letter to join the study agreed and attended the hospital for a single visit. During this visit an andrological examination was performed which included measurement of the flaccid stretched penile length, and the assessment of the testis size by comparison with a rosary of ovoids. A seminal analysis was performed according to the WHO manual for semen analysis.⁹ A blood sample was obtained for hormonal assay and the serum was frozen and stored at -20°C for later analysis. Plasma follicle stimulating hormone (FSH) and luteinising hormone (LH) were assayed using the Chelsea LH and FSH solid phase kit. The plasma testosterone levels were measured using an in house radioimmunoassay extraction.

The six males who refused to participate in the study had an age range of 19 to 34 years. Three of these men had undescended testes and another man had fathered four children (three of them had Noonan syndrome).

Results
All the men who attended were already known to have Noonan syndrome. Nine of them had short stature. The clinical features and labora-

Table 1 Clinical features in 11 adult males with Noonan syndrome

	Patient										
	1	2	3	4	5	6	7	8	9	10	11
Small stature	+	+	+	+	-	+	-	+	+	+	+
Characteristic facies	+	+	+	+	+	+	+	+	+	+	+
Hypertelorism	-	+	+	+	+	+	+	+	-	+	+
Downward slanting eyes	+	+	-	+	+	+	+	+	+	+	+
Epicanthic folds	-	+	+	-	+	+	+	+	+	+	+
Ptosis	+	+	+	-	-	+	+	+	+	+	+
Low set ears	+	+	+	+	+	+	+	+	+	+	+
Refractive errors	+	+	+	-	-	+	+	+	+	+	+
Short neck	+	-	-	+	-	-	+	-	+	+	+
Webbing	+	+	-	+	-	-	+	-	+	+	-
Low posterior hair line	+	+	-	+	-	+	+	+	+	+	+
Pectus excavatum	+	+	+	+	-	+	+	+	+	+	+
Pectus carinatum	+	+	+	-	-	+	+	+	-	+	+
Cubitus valgus	+	-	-	-	-	+	+	+	+	+	+
Scoliosis/kyphosis	+	+	-	-	-	-	-	-	+	-	+
Congenital heart disease											
PS	-	+	+	-	-	-	+	+	+	-	-
Cardiomyopathy	+	-	-	-	-	-	-	-	+	-	-
Other	-	-	-	-	-	-	-	+	-	+	+

Table 2 Genital tract function in 11 adult males with Noonan syndrome

	Patient											
	1	2	3	4	5	6	7	8	9	10	11	
Age (completed years)	47	21	22	31	41	45	19	18	19	25	40	
Bilateral testicular maldescent	—	—	—	—	—	+	+	+	+	+	+	
Delayed puberty	—	+	+	—	—	—	—	—	—	+	—	
Testicular volume (ml) R&L (N > 15 ml)	20 20	15 15	25 25	20 25	25 25	15 25	25 25	20 20	25 25	0 15	15 15	
Penile length (cm) (N = 13.3, SD 1.6)	10	12	13	11	13	10.5	11.5	12	10	10	12.5	
Vasectomy	+	—	—	—	+	—	—	—	—	—	—	
Fatherhood	F*,F	—	—	M*,M	M*,F*,F*	M*,M	—	—	—	—	—	
Sperm concentration (m ml)	N A	—	—	61	N A	N A	< 1	Azoo	—	Azoo	Azoo	
FSH (N = 1–7 IU l)	1.6	2.9	4.8	4.3	5.5	19.6	30	20	3.6	36.1	28.2	
LH (N = 1–10 IU l)	4.8	3.4	5.6	3.6	5	11	8.7	7.2	3.9	7.7	13.1	
Testosterone (N = 9–24 nmol l)	9	11.4	22.8	26.4	18	20.4	27	41.4	11.4	19.8	9.6	

* = Affected with Noonan syndrome, M = Male, F = Female.
N A = Not available post vasectomy.

tory findings are summarised in tables 1 and 2. The mean age was 29.5 (SD 11) years (range 18–47). Testicular maldescent had occurred in six of the men and puberty was delayed in three (one with maldescent). The stretched penile length was 11.4 (SD 1.2) cm (range 10–13) and the mean testis volume was 21 (SD 4) ml (range 15–25). No patient reported any sexual difficulty, but the onset of sexual activity was delayed in men with late onset of puberty. The results of the hormone studies are shown in table 2. LH and testosterone levels were essentially normal in all patients, but the FSH levels were grossly raised in all men with testicular maldescent with the exception of one man who had normal sized testes. Four of the men had married (Nos 1, 4, 5, and 6), and had fathered children. Noonan syndrome occurred in their offspring confirming paternity. Three of them had undergone a vasectomy, and the fourth was able to produce a normal semen sample. Only one of these fathers (No 6) belongs to the group with testicular maldescent. He had normal sized testes, but a raised FSH level. The other four men with history of maldescent had azoospermia (3) or severe oligozoospermia (1), with raised plasma levels of FSH. It should be noted that two single men aged 21 and 22 with a history of delayed puberty were unable to produce a sample of semen at the time of their visit.

Of the original sample of 17 men contacted, nine had undescended testes and only one of them (11%) fathered children. Four of the remaining eight men with normal descent had children.

Discussion

There has been a paucity of published reports dealing with the genital function in males with NS.^{10,11} Some of these were isolated case reports which looked at the hormonal profile of the patient or studied his testicular function.^{4,12}

Theintz and Savage⁵ reported five prepubertal boys with NS who had all undergone orchidopexy in early childhood. They found them all to have delayed skeletal maturation and pubertal development with an exaggerated LH response. The possible mechanism suggested is Leydig cell dysfunction. Saez *et al*¹³ were unable to find evidence for this in their study. They estimated plasma testosterone,

dehydroepiandrosterone and its sulphate in two males with NS before and after administration of human chorionic gonadotrophin (HCG). Their age was 10 and 17 years and both had normal testicular descent. Both patients had a sharp rise in plasma testosterone after stimulation with HCG.

Sinisi *et al*¹⁴ studied four men with Noonan syndrome. Their age ranged from 19 to 23 years and two of them were mentally retarded with cryptorchidism. He found that the two with normal testicular descent had normal levels of FSH and LH. One of them had normal semen analysis. In contrast the two men with testicular maldescent had high levels of LH, and one had high FSH, and the only semen test showed azoospermia.

Kumanov¹⁵ in 1985 studied four Noonan males aged 19 to 27, none of whom had mental retardation. He mainly described their hormonal profile. One patient was normally virilised and had normal sexual function. Seminal analysis was only available in this patient and was within normal limits. Two patients had prepubertal testicular size, while the fourth had bilateral undescended testes. High levels of TRH and prolactin were found in all of them.

Okuyama *et al*¹⁶ studied the gonadal function in seven prepubertal cryptorchid boys with NS and found abnormalities of testicular function. Their age ranged from 5 to 16 years. Five of them had mild mental retardation. They all had LHRH and HCG stimulation and testicular biopsy. The histology in all testes showed interstitial fibrosis and four of seven had abnormalities of seminiferous tubules. Two of the seven had good response to hormonal stimulation. Testicular volume was reduced in six of seven, and one case showed early pubertal changes. This is not surprising as this patient was the oldest of the group.

In the present study we found no evidence of any Leydig cell deficiency, even in the men with testicular maldescent. Six of 11 men had a history of testicular maldescent and these patients had poor quality semen associated with a high level of plasma FSH, suggesting a failure of spermatogenesis. In contrast, men with normal descent had normal FSH levels and tended to be fertile. Penile length tended to be shorter than average, but no patient had a

micropenis (average -2.5 SD), nor did any man report any sexual problems related to penile length.

It has been shown that pubertal development is delayed in both sexes in Noonan syndrome. The mean age (SD) of menarche in 20 postpubertal women with Noonan syndrome was 14.6 (1.17) years.⁸ Fertility does not appear to be affected in females. Most familial cases that have been reported have shown an overrepresentation of affected mothers. In our previous study, we had 16 familial cases, and in 12 of them the mother was the affected parent. The decreased paternal transmission is likely to reflect the impairment of fertility in males. In the clinical study of Char *et al*¹⁷ of 45 cases of Noonan syndrome there were five familial cases, and in three of them this was because of mother to daughter transmission. Nora *et al*¹⁸ described three families and in all three the condition was transmitted through the mother.

Maldescent is recognised to be an adverse factor on male fertility, and this is the case in men without Noonan syndrome. Chilvers *et al*,¹⁹ in a review of published reports, found that 75% of men had azoospermia or oligozoospermia following orchidopexy for bilateral undescended testes.

In conclusion, it appears that the main factor leading to impairment of fertility in men with Noonan syndrome is the presence of bilateral cryptorchidism. In this study the mean age at orchidopexy was 5.5 years. It remains to be seen whether earlier surgery would improve the outcome. In the presence of normally descended testes, men with Noonan syndrome are likely to be fertile.

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