

THE ROLE OF THE NEWBORN SCREENING PROGRAMME (NSP) FOR THE DIAGNOSIS OF A 17-YEAR-OLD BOY WITH CONGENITAL ADRENAL HYPERPLASIA (CAH) DUE TO 21 OH DEFICIENCY

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ABSTRACT

A newborn boy was diagnosed with CAH via the 2010 implemented NSP in Bulgaria. The 17-OH-progesterone (17-OHP) from the 1st filter paper card (FPC) was 44.6 nmol/l, from the 2nd FPC 80 nmol/l. The examination on day 15th revealed as “only” sign slight hyperpigmentation of the scrotum. The screening suspicion “classical CAH” was confirmed by the increased serum levels of 17-OHP (normal electrolytes) and treatment with hydrocortisone was started. The MLPA analysis revealed a hemizygous del3-4, c.622T>A; p.I173N. Family history: 2nd son of relatively short parents – mother’s height – 152 cm (SDS_h = -2.12), father’s height – 164 cm (SDS_h = -1.96), MPH- 158 cm, SDS_{MPH} = -2.54. The height of his *older brother* is 157 cm (SDS_h = -3.01), while his target height of 164.5 cm (SDS_h = -1.88) was markedly above the actual height. At 7 years he had initial pubarche and was the tallest boy in his class. He was taller than the average for his age until 12 years then he stopped growing. The older boy was also brought to a pediatric endocrinologist at 17 years of age. Elevated levels of 17-OHP in the serum >60 nmol/l (157.4) and on FPC:>285 nmol/l (537), together with the genetically verified CAH in the younger brother lead to the diagnosis “simple virilizing 21 OHD”, so treatment with hydrocortisone was started.

CONCLUSION: Some of the simple virilizing forms of CAH may remain unrecognized, esp. in “index-families”. The newly implemented CAH NSP represents a useful diagnostic tool also in such cases. Ultrasound of the adrenals and testes for testicular rest tumors is important initially and during follow up.

Keywords: simple virilizing 21 OHD - CAH, screening, late diagnosis in males

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INTRODUCTION

Congenital adrenal hyperplasia results from autosomal recessive inherited defects in cortisol biosynthesis. More than 90% of cases are caused by 21-hydroxylase (21-OH) deficiency, found in 1:10 000 – 1:15 000 live births worldwide. The measurement of 17-OH progesterone (17-OHP) in dried blood spots worldwide showed its effectiveness in the early diagnostic of CAH caused by classic 21-OH deficiency.

cy. CAH is a disease suitable for newborn screening because it is common and potentially fatal. Early recognition and treatment can prevent morbidity and mortality, therefore universal screening for CAH is recommended by the ESPE and LWPES (15). In Bulgaria it was introduced in 2010 as part of the National neonatal screening programs and the first results show a preliminary incidence 1:9266 (16). Data on CAH incidence beforehand were lacking. Some of the cases are familial, allowing to expect that the screening program could contribute for establishing the diagnosis in other family members as well.

AIM

With the following case of a 17-year-old boy, diagnosed with simple virilizing CAH after the birth of an affected brother, we would like to draw attention to the missed opportunities for early recognition of the disease, the negative impact of the late diagnosis on the final height, the prevention of

further complications and the problems of transition to the internal medicine endocrinologists.

CASE PRESENTATIONS

Patient 1 (T.J.G.) was born in 1995 from a first uneventful pregnancy of healthy parents through Caesarian section because of coiled cord. His birth weight – 3500 g and birth length – 50 cm were on the 50th percentile. The postnatal period was normal, except for prolonged jaundice.

The **family history** was unremarkable, but the parents were relatively short: mother's height- 152 cm ($SDS_h = -2.12$), father's height- 164 cm ($SDS_h = -1.96$), midparental height (MPH)-158 cm, $SDS_{MPH} = -2.54$, target height is 164.5 cm ($SDS_h = -1.88$).

Growth and development:

He was a healthy boy, with normal psychological development. His growth up to 2 years of age was within the normal range (see Fig. 3), but the height velocity sharply increased after the second year (see Fig. 1 - Growth velocity of T.J.G.) At 7 years he was the tallest boy in his class with initial pubarche and mutation of the voice (see Fig. 2 - Growth curve of T.

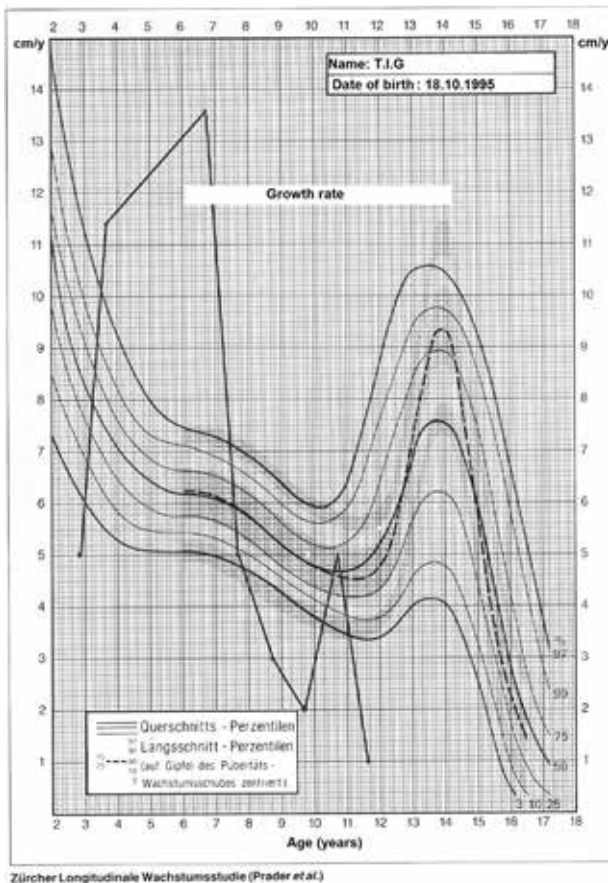


Fig. 1. Growth velocity of T.J.G.

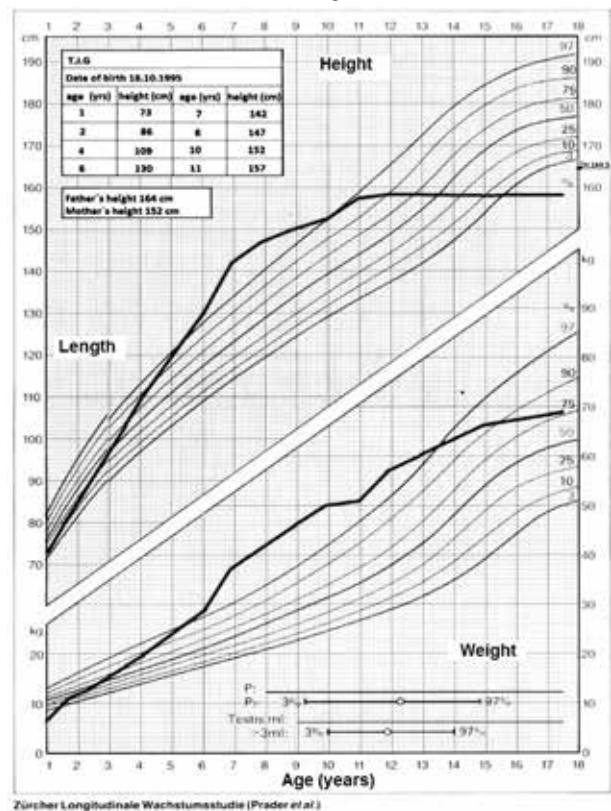


Fig. 2. Growth curve of T.J.G. from 1 to 17 years

J. G. from 1-17 years). At eleven significant pubarche and axillarche were noticeable. He grew rapidly until 12 years of age, when moustaches appeared, then linear growth stopped. He had already reached his final height -158 cm, SDS_H= -3.01 (see Fig. 2- Growth curve of T.J.G. from 1 to 17 years).

Diagnosis:

His *younger brother* (patient 2, D.J.G.) was born, when he was 17 years old. The baby was seemingly healthy, with birth weight - 3600 g and birth length - 50 cm (50th percentile), but pathologic results from the NSP were reported. The 17-OHP from the 1st filter paper card (FPC) was 44.6 nmol/l (ISNS reference range-20), from the 2nd FPC- 80 nmol/l and from the 3rd-201.6 nmol/l. Because of the sharply increasing 17-OHP, a consultation with a paediatric endocrinologist was accomplished on the 15th day, and revealed as “only” sign slight hyperpigmentation of the scrotum. The screening suspicion was confirmed by the increased serum levels of 17-OHP, while the electrolytes were normal: 17-OH Progesterone > 60 (120) nmol/L (6.1±2.4), Testosterone- 4.24 nmol/l (4-14 nmol/l), Na- 133 mmol/l (136-145), K- 5.97 mmol/l (3.5-5.1), Glucose -3.9 mmol/l (3.5-5.5). Hydrocortisone treatment was started from the 15th day. The diagnosis simple virilizing CAH was confirmed by a molecular genetic analysis. The multiplex ligand dependent probe amplification (MLPA) and sequencing analysis revealed a hemizygous deletion 3-4 and a point mutation c.622T>A; p.I173N. Normal growth was observed during the first 18 months (see Fig. 4 - Growth curve of D. J. G. up to 1 1/2 years).

The parents were informed in details about the course of the disease and the pitfalls of over- and undertreatment. In the course of the interview, they shared their concern about the growth of their older son. The auxological data from his records were requested and the older boy was also brought to a pediatric endocrinologist several months later. He seemed clinically healthy, with athletic constitution. The X-ray of the wrist showed fused epiphyses. Elevated levels of 17-OHP in the serum > 60 nmol/l (157.4) and on FPC: > 285 nmol/l (537), together with the verified CAH in the younger brother lead to the diagnosis “simple virilizing 21 OHD”. At the time of diagnosis he had normal testosterone - 15 nmol/l. Substitution with hydrocortisone was started at 17 years

of age with initial dosage- 20 mg / 24h. The diagnosis was a shock for the patient and his family. The boy had expectations that the treatment will promote his further growth and was frustrated about the poor height prognosis. This led to a bad compliance and at some point he stopped the treatment completely. An ultrasound of the adrenals and testes was carried out shortly before his 18th birthday. No testicular adrenal rest tumors (TARTs) were detected. At 18 years of age, according to the country legislation, his care should be transferred to an internal medicine endocrinologist.

DISCUSSION

The diagnosis of simple virilizing CAH in boys is a challenge, especially before the advent of the newborn screening programmes. Boys with classic CAH have no signs of the disease at birth, except subtle hyperpigmentation, as our patient 2, and possible penile enlargement. They may present with early virilization at age 2-4 years (9).

Growth aspects

Until recently, it was generally perceived that children with CAH would ultimately be short as adults and invariably below their genetic potential. However, studies over the last ten years have contrasted this idea, suggesting that most children with CAH will have a final height (FH) below their target height but within 2 standard deviations (SD) of the mean (11). Although this comparison is not very suitable for our patient 1, because of the low SDS of the TH, a variation of - 1.13 SDS between the TH and FH shows the deleterious effect of the very early growth spurt. Critically important time periods of growth in all children are infancy, early adolescence and puberty. Interestingly, the negative effect of androgen excess on growth and skeletal maturation seen in later childhood does not occur during infancy. A report from Sweden on the physical development in 15 children with no or insufficient treatment showed no growth acceleration or virilization until after 18 months of age (17). A study from the Netherlands on 17 children with untreated simple-virilizing CAH revealed no increased height velocity in the first 12 months of life (5). These observations indicate that growth during the first 1.5 years is not very sensitive to androgens (5,17) and that sub-optimal control could be tolerated at that age regard-

ing the final height (4). The early growth curves of our two patients, one of them treated early and the other untreated, are quite similar and are consistent with these data (see Fig. 3 - Growth curve of T.J.G up to 2 years and Fig. 4 - Growth curve of D.J.G up to 1 ½ years).

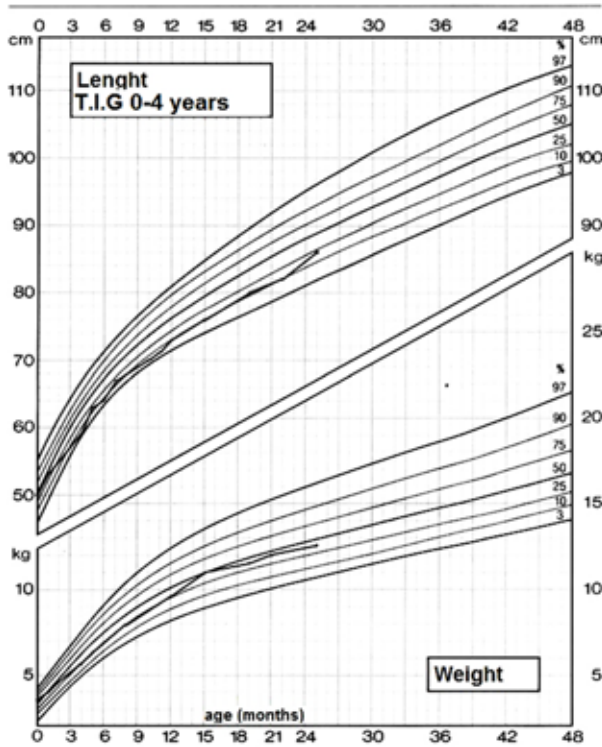


Fig. 3. Growth curve of T.J.G up to 2 years

Boys with simple virilizing CAH are more prone to impaired height, because, on one hand, they are more likely to be diagnosed late and on the other, they have increased sensibility to aromatized estrogens from adrenal androgens and this could contribute further to the early fusion of the growth plates (12). Sometimes the clinical signs are noticed, but not recognized as pathological. Such was the case of T.J.G, who had conspicuously accelerated growth and precocious pubarche. Unfortunately, neither of these signs was brought to a specialist's attention.

Puberty

The precocious pubarche can be defined as pubic hair onset before the age of 8 in girls and 9 in boys. In most of the cases, it is related to nonpathological precocious secretion of adrenal androgens,

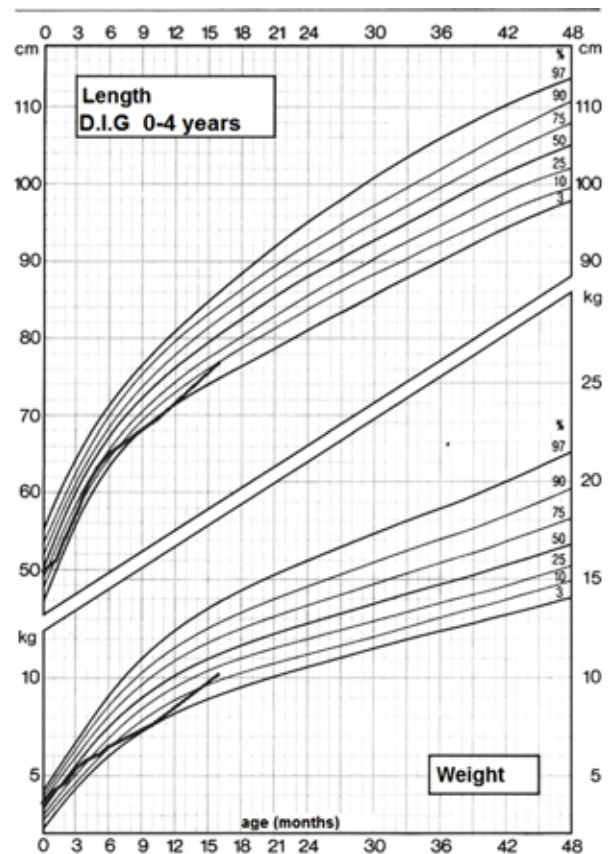


Fig. 4. Growth curve of D.J.G up to 1 ½ years

but in 5-20 % the cause is non-classical congenital adrenal hyperplasia. It always necessitates overall clinical examination and assessment of the growth velocity and bone maturation. Many authors recommend an ACTH test, while Armengaud et al. prefer a selective strategy, based on a basal 17-OHP level (2). In non-classical CAH, growth acceleration is small, but bone maturation is more pronounced (13).

Delayed diagnosis in the boys with classical CAH is invariably associated with progressive virilization (precocious pseudo-puberty), with markedly advanced bone maturation. Chronically elevated adrenal androgens can lead to early maturation of the hypothalamo-pituitary-gonadotrophin axis (7). When advanced bone maturation has reached the average age of the onset of puberty, the latter begins. In other circumstances, the hypothalamo-pituitary axis may be down-regulated by high levels of testosterone produced by the peripheral metabolism of the adrenal precursors. When treatment is started, testosterone is suppressed, thus the feedback loop

opens and central puberty starts (6). Unfortunately we lack reliable data on the pubertal development in our patient, except the precocious pubarche. The very early maturation permits speculations whether the androgen excess is the only culprit for the short adult height, but the small peak at his growth velocity curve between 10 and 11 years of age probably reflects his blunted pubertal growth spurt, occurring at the physiological age.

Complications and treatment of CAH in adult life

CAH is a life-long chronic disorder. In childhood, treatment is focused on issues of gender assignment and optimization of growth and pubertal development. Priorities change with increasing age, typically focusing on fertility in early adult life and prevention of metabolic syndrome and osteoporosis in middle and older age (1). The reduced fertility in men is associated mainly with TARTs or sometimes with suppressed gonadotrophin secretion due to adrenal androgen excess (14). TARTs can be detected from childhood in boys with inadequately controlled classical CAH (8). They are ACTH dependent, and their growth can be reversed by suppressive glucocorticoid treatment. They originate from adrenocortical remnants in the testes. TARTs are of special concern in our patient, because of the long standing ACTH stimulation.

There is still no consensus for management of adults with CAH. Probably this will soon be changed because the number of patients is increasing. With the glucocorticoid treatment and the newborn screening programmes, the majority of children with 21-hydroxylase deficiency are reaching adulthood (3). For adults, clinicians may use hydrocortisone, prednisone, prednisolone, dexamethasone, or a combination of treatments. Practice varies worldwide. An UK survey of 30 teaching centers, showed a variety of different regimens to treat CAH adults; hydrocortisone was the most common, followed by dexamethasone and then prednisolone. Sixty percent of practitioners used a reverse circadian pattern of glucocorticoid administration. Patient-related factors often determine the specific regimen (10). New preparations with fast and delayed hydrocortisone release are developed.

CONCLUSIONS

Some of the simple virilising forms of CAH may remain unrecognized, especially in “index-families”. The newly implemented CAH NSP represents a useful diagnostic tool also in such cases. Initially and during follow up ultrasound of the adrenals and testes for testicular rest tumors is important.

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