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HONG KONG SEPTEMBER 2017

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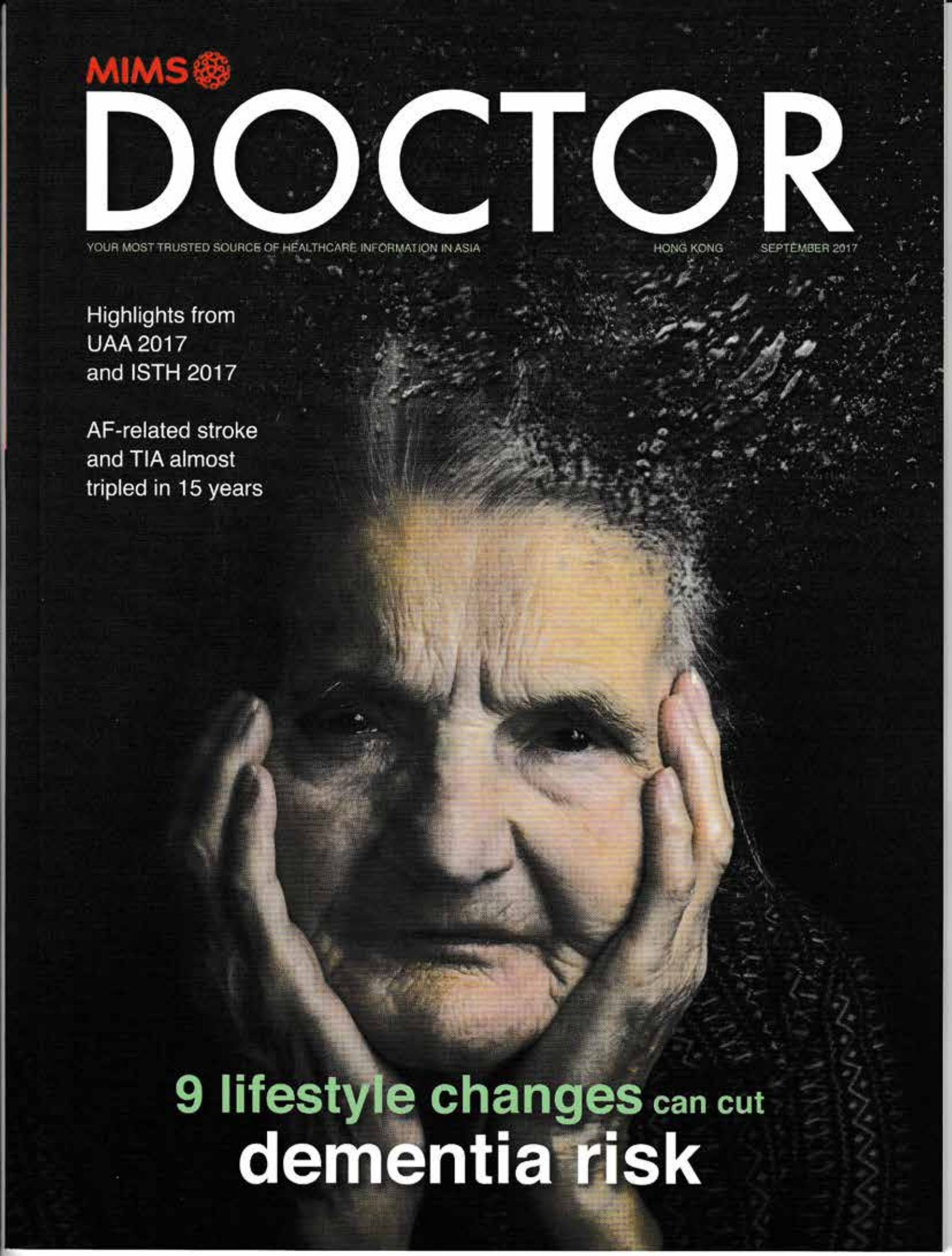


9 lifestyle changes can cut dementia risk

Dr Pik-Shun Cheng

Benefits of GH treatment in children born small for gestational age

Children born small for gestational age (SGA) who do not show spontaneous catch-up growth by 2 years of age generally remain short for life. Although the majority of them are not growth hormone (GH)-deficient, GH treatment has been shown to improve growth in this population. In a recent interview, Dr Pik-Shun Cheng, Specialist in Paediatrics in private practice in Hong Kong, discussed the role and benefits of recombinant GH (Saizen®, Merck) supplementation, and shared her clinical experience in the management of short stature in children.

The risk of having a short final height (<-2 standard deviation scores [SDS]) is five times higher for children with a low birth weight and seven times higher for those with a low birth length compared with children with a normal birth size. [*Horm Res* 1998;49 (suppl 2):7-13]

GH has been shown to increase final height to within the normal range in children born SGA and in other disorders, such as GH deficiency, idiopathic short stature, Turner syndrome, chronic renal insufficiency, and Prader-Willi syndrome.

GH treatment in children born SGA

"The mechanism of action of GH in children born SGA is unclear, but it is assumed that some of them have hypersecretion of GH during the initial catch-up growth period in the first 6 months of life. For those 10 to 15 percent who do not catch up, we need to consider GH to induce catch-up growth," suggested Cheng.

Diagnosis and therapy initiation

According to Cheng, roughly 2.3 to 3.0 percent of Hong Kong's population are born SGA, indicating it is not uncommon. "The statistical definition of SGA is based on a birth length or a birth weight of <-2 SDS," she explained. "A survey by the Chinese University of Hong Kong showed that the average birth weight of local babies was 3.11 kg and average birth length was 50 cm. Therefore, if the baby's weight is <2.5 kg and/or birth length is <45 cm, it is considered SGA." [http://www.healthy-hk.gov.hk/phisweb/plain/en/health_info/vit_stat/birth_weight/]

GH has been licensed for the treatment of children born SGA who have not exhibited catch-up growth by 2 years of age (in the US) or by 4 years of age (in Europe). "There are no local guidelines in Hong Kong on how to manage children born SGA, but we monitor their growth routinely. In my practice, I usually consider GH from 4 years of age onward," she said.

In the past, low awareness among Hong Kong parents regarding the issue of short stature might have caused delays in treatment initiation. "For example, teens with short stature would come to my clinic, and we would discover from their history that they were

Table. Final height for children born SGA treated with GH

Reference	No. of patients	Age at baseline, years	Dose*, mg/kg/week	Treatment duration, years	Height SDS, mean±SD			p value† or (95% CI)
					Baseline	Final	Gain	
Ranke & Lindberg, 1996[1]	16	12.7‡	0.23	4.3‡	−2.7‡	−1.7‡	1.0‡	ND
Albanese, et al, 1998[2]	12	7.6±2.1	0.37	8.5	−3.0±0.7	−1.5±1.0	ND	<0.001
Coutant, et al, 1998[3]	70	10.7±2.5	0.13	4.6±2.5	−2.9±0.8	−2.0±0.7	0.9±0.8	ND
	Control: 40	10.0±3.4	–	–	−2.8±0.7	−2.2±0.1	0.6±0.9	ND
Chatelain & de Zegher, 1999[4]	19	11.5‡	0.21	6.8‡	−3.2‡	−2.2‡	ND	ND
Zucchini, et al, 2001[5]	29	10.9±0.4§	0.24	4.6	−2.3±0.1§	−1.8±0.2§	ND	ND
	Control: 20	10.7±0.6§	–	–	−2.0±0.1§	−1.9±0.2§	ND	ND
Carel, et al, 2003[6]	91	12.6±1.5	0.47	2.7±0.6	−3.2±0.6	−2.0±1.0	1.1±0.9	0.002
	Control: 33	12.9±1.4	–	–	−3.2±0.6	−2.7±0.9	0.5±0.8	NS
van Pareren, et al, 2003[7]	28	7.9±1.9	0.23	7.9±1.7	−2.9±0.8	−1.1±0.8	1.8±0.7	<0.001
	26	8.2±1.9	0.47	7.5±1.7	−3.0±0.7	−0.9±0.8	2.1±0.8	<0.001
Clayton, 2003[8]	24	ND	0.23	>8	<−2.5	ND	1.90	(1.49-2.30)
	32	ND	0.47	>8	<−2.5	ND	2.19	(1.85-2.53)
Rosilio, et al, 2005[9]	20	9.6±0.9	0.47	≥2¶	−2.6±0.5	−2.0±0.8	0.7±0.8	<0.001

*GH doses were all converted to mg/kg/week using 1 IU=3 mg and 1 m^2/27.25=1 kg body weight.
†Final vs baseline.
‡Median values.
§Standard error.
¶Treatment for 2 years followed by 2 years off-treatment; treatment was resumed up to final height in n=4 patients.
CI = confidence interval; GH = growth hormone; ND = not determined; NS = not significant; SD = standard deviation; SDS = standard deviation score; SGA = small for gestational age
Adapted from: 1) Acta Paediatr Suppl 1996;417:18-26; 2) Horm Res 1998;50 (suppl. 3): P91, abstract; 3) J Clin Endocrinol Metab 1998;83:1070-1074; 4) Growth hormone treatment in children with intrauterine growth retardation and Silver-Russell syndrome. In: Ranke MB, Wilton P, eds. Growth Hormone Therapy in KIGS. Johann Ambrosius Barth Verlag: Leipzig 1999; 5) Arch Dis Child 2001;84:340-343; 6) J Clin Endocrinol Metab 2003;88:1587-1593; 7) J Clin Endocrinol Metab 2003;88:3584-3590; 8) Clayton P, 42nd Annual Meeting of the European Society for Paediatric Endocrinology (ESPE), 2003; 9) Eur J Endocrinol 2005;152:835-843.

born SGA," she said. "Nowadays, with more education and awareness, parents seek treatment earlier, probably when the children are around 3 or 4 years of age."

Dosage, treatment duration and managing "catch-down" growth

GH is administered by daily subcutaneous injection, preferably in the evening. The dosage is individually determined based on the patient's body surface area or body weight. "Based on the literature, we prescribe 40 to 60 µg/kg/day," said Cheng.

The majority of patients are using the GH autoinjector, a convenient and easy-to-use device. "The autoinjector is preprogrammed with the correct dose. You just insert the cartridge and press, and the dose is released automatically," said Cheng. "Importantly, the autoinjector has memory, so we can monitor compliance, which is particularly important for adolescents who inject themselves. You hook it up to a computer and download all the data, so monitoring any missed doses is easy, increasing treatment reliability and compliance."

"Long-term continuous GH therapy can significantly increase final height to within the normal range"

GH treatment duration is usually given from the time of diagnosis until puberty, where a spontaneous boost in height takes place. "One problem usually encountered with GH therapy is something we call 'catch-down' growth, which happens after ceasing treatment with GH. The reason behind this phenomenon is still unclear. The strategy we employ to diminish this is by continuous long-term GH treatment, while keeping the off-treatment periods to a minimum," suggested Cheng. [*J Clin Endocrinol Metab* 2004;89:1234-1239]

Efficacy and safety

Studies have demonstrated that treatment with GH can induce sustained catch-up growth in young children born SGA, and long-term continuous GH therapy can significantly increase final height to within the normal range. (Table) [*Acta Paediatr* 1998;87:511-517; *Adv Ther* 2008;25:951-978]

"Most studies have demonstrated an increase in final height. In general, the earlier the children are started on GH and the longer the treatment period, the better the effect. Successful GH

treatment relies on regular and continued injections," Cheng pointed out.

In all reported studies, GH was well tolerated, even at high doses. Two large observational studies of patients treated with GH for different indications have raised no unexpected safety concerns for SGA patients. [*J Clin Endocrinol Metab* 1996;81:1704-1710; *Horm Res* 2007;68 (suppl 5):41-47]

In Cheng's experience, the most common side effect reported by GH-treated children is growing pain. "This may occur in any child during growth spurts. Usually they tolerate it quite well and it will resolve spontaneously," she said. "Some patients have fluid retention at the beginning of treatment, but it's rare in my experience."

Another rare but serious adverse event is slipped capital femoral epiphysis (SCFE), which may also occur in growing children without GH therapy. "It's a growth-related problem. Clinical suspicion is advised in children complaining of unilateral pain in the hips or knees, and treatment is either bed rest or surgical, depending on the severity," said Cheng.

Other GH-related adverse events include increased intracranial pressure, disturbances in glucose metabolism, and hypertension. "We need to monitor and watch out for those problems, although they are quite rare," she suggested. "Studies looking at cancer risk found no increased risk in GH-treated patients."

Clinical considerations

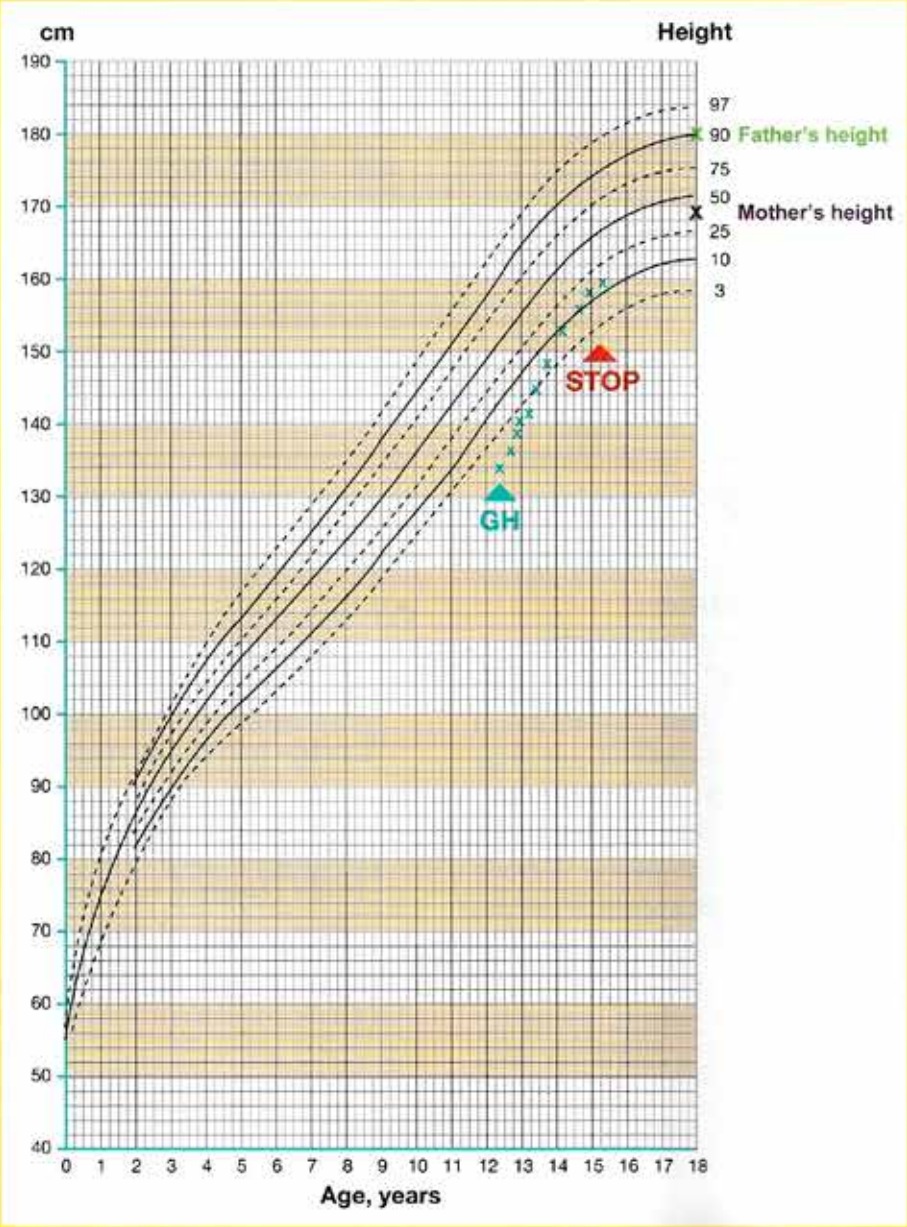
Physicians who encounter paediatric patients with short stature (<-2 SDS) are advised to review their medical history for SGA. Children born SGA should be referred at an early age to consider GH treatment, as studies have shown that long-term, continuous GH therapy until puberty might improve their chances of achieving final height within the normal range.

Case report

A 12-year-old boy presented with short stature. His height was <3rd percentile and bone age was <11 years. Parents' height values were within the normal range. Previous investigations in a public hospital showed normal levels of GH. Despite being born SGA, the patient had not received treatment because SGA is not an approved indication for GH treatment in the public healthcare system. The patient was started on GH and continued treatment for about 3 years. Routine tests for insulin sensitivity and hyperglycaemia were normal.

The patient experienced significant catch-up growth, his height reaching the 10th percentile at 15 years of age. (Figure) Given that the treatment period overlapped with puberty, the catch-up growth in the first year can be attributed to GH treatment. At puberty, the growth was probably the effect of GH treatment together with the sex hormones. At follow-up around the age of 17 years, the patient's height was 162 cm, and the estimated final height was around 165 cm.

Figure. The patient's growth chart



GH = growth hormone