Breakthroughs in Congenital Adrenal Hyperplasia Care – Hope on the Horizon

Nishant Raizada, SV Madhu

Department of Endocrinology, Centre for Diabetes, Endocrinology and Metabolism, University College of Medical Sciences and GTB Hospital, Delhi, India

Since the reporting of the first probable case of congenital adrenal hyperplasia (CAH) back in 1833, we have come a long way in understanding and treating this not-so-rare disease.

While the global prevalence of the classic form of CAH is between 1 in 14 000 and 18 000 live births, the ICMR Taskforce data from India report a prevalence of 1 in 5762 births.[1] This higher prevalence in India may be attributed to higher consanguinity, although whether there are some genetic factors at play is still debatable. While most data are derived from neonatal screening programs, data from the Danish nationwide population-based registry, which includes patients diagnosed later in life, report a combined prevalence of CAH of 15.1 and 9.0 per 100,000 births for females and males, respectively.[2]

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency manifests a wide phenotypic spectrum based on the degree of residual enzyme activity. The active gene, CYP21A2, and its pseudogene, CYP21A1P, are located 30 kb apart on the 6q21.3 region and share approximately 98% sequence homology in the coding region. This high homology leads to frequent micro-conversions and large rearrangements through intergenic recombination, complicating genetic testing. Consequently, genetic testing for CAH should include an evaluation of copy number variations and Sanger sequencing to accurately identify mutations and establish genotype–phenotype correlations. A variety of genetic defects have been reported in CAH. The homozygous c.293-13A/C > G (I2G) genotype was the most common in a study from Australia affecting 15% of cases of 21 hydroxylase deficiency.[3] In an Italian cohort, the most prevalent genetic variant in the non-classic CAH was the p.Val282Leu (51.3%), while in the classical CAH, c.293-13C > G (26.0%) was the most common. A comprehensive review of the genetics of CAH reported from India indicates that p30L, I172N, and I2G variants are common in Indians. In line with the higher CAH prevalence in India, at least 13 novel variants have been reported in Indian studies so far.[4] These data indicate that more genetic studies should be performed in Indian patients to elucidate the reasons for the higher prevalence better. These data also assist in establishing genotype–phenotype correlation, which are crucial for guiding early treatment, predicting clinical phenotype and prognosis, and providing genetic counselling. Phenotypic variability was seen with P30L, I2G, and I172N mutations. Individuals with the same compound mutations may have different phenotypes based upon their gender.[5] The availability of genotypes can provide the basis for pre-natal testing. Pre-natal diagnostic testing can be offered if both parents are carriers of CYP21A2 mutations with amniocentesis or chorionic villus sampling being the usual diagnostic modalities. More recently, cell-free foetal DNA from maternal blood has also been employed as a non-invasive diagnostic modality. The families at very high risk of CAH may be offered *in vitro* fertilization with pre-implantation genetic testing, although there may be ethical concerns in this approach.[6]

The management of CAH has always been a tight-rope walk with the clinician balancing underdosing (with resulting adrenal androgen excess) and overdosing (with associated metabolic and cardiovascular adverse effects) of glucocorticoids. The preferred drug is hydrocortisone as it has a better adverse effects profile as compared to other glucocorticoids. But the short half-life of hydrocortisone mandates multiple doses per day and many patients, especially adolescents, may not maintain adequate adrenal androgen control with hydrocortisone. Other glucocorticoids, such as prednisolone and dexamethasone, provide the convenience of less frequent dosing and better androgen control, but the adverse metabolic effects render them unsuitable for most patients, especially children and adolescents.

Several efforts have been made to modify hydrocortisone delivery to improve the compliance and androgen control. Plenadren, a sustained-release hydrocortisone formulation, has been devised for use in adrenal insufficiency with a once-daily dosing, but there are limited data upon its use in CAH. Furthermore, it is unlikely that a single morning dose will be able to control the early morning ACTH surge. A different sustained-release preparation is Chronocort, which exhibits a delayed but prolonged action. Twice-daily Chronocort has shown potential in mimicking the early morning rise in cortisol and providing more physiological cortisol levels in the day. Initial data suggest that Chronocort can provide better biochemical control along with a reduction in glucocorticoid dose in adult CAH patients.[7] Modified-release hydrocortisone tablets showed a greater reduction in 17 hydroxy-progesterone (17-OHP) levels as compared to prednisolone, and the dose of the hydrocortisone could be reduced in many cases.[8] Crinecerfont, an oral corticotropin-releasing factor type 1 receptor antagonist, has shown promise in terms of reduction in androstenedione levels and reduction in the glucocorticoid dose to physiological levels

in both adults and children.[9,10] More than 60% adults could maintain control of adrenal androgens with physiological glucocorticoid replacement doses while on crinecerfont as compared to placebo. Crinecerfont showed a 18% reduction in mean glucocorticoid dose in the paediatric age group. Furthermore, drugs such as abiraterone (a CYP17A1 inhibitor) and a combination of testolactone and flutamide are being studied with the aim of providing lower and more physiological glucocorticoid doses and optimizing height outcomes in children with CAH. Growth hormone therapy, with or without GnRH analogues, has also been used to improve height outcomes, but most such studies were small and did not have a control group.[11] The future of CAH treatment includes modalities like cell-based therapies and gene-based therapies where cells or genes producing the deficient enzymes can be introduced into the patient's body.

In this issue, Boyareddy *et al*.[12] report the clinical and hormonal profiles of 27 patients with CAH including adults and children. They noted a high prevalence of obesity among CAH patients including both adults and children. A majority of their patients had consanguinity, and a quarter of them had short stature. Around half of their patients had sub-optimal 17 OHP levels, indicating the difficulties in achieving appropriate glucocorticoid doses. Furthermore, one patient developed testicular adrenal rest tumour, while five episodes of acute adrenal crisis were reported. Their data indicate that despite the best efforts at its management, several complications plague the life of CAH patients. Studies have reported that adult females with CAH are more likely to be overweight and have insulin resistance, diastolic dysfunction, and poor quality of life, while males suffered from autistic and cognitive issues.[13,14] Some data suggest that adolescents and young adults with CAH have more abdominal and visceral obesity as compared to controls.[15] In a population which is predisposed to obesity, metabolic syndrome, and dysglycaemia, the added impact of glucocorticoid therapy can dramatically increase morbidity and mortality. CAH may be associated with other cardiovascular risk factors such as hypertension, dyslipidaemia, and atrial fibrillation. A meta-analysis has reported higher insulin resistance in CAH patients as compared to controls.[16] In fact, the Swedish registry data indicate that cardiovascular diseases are the second most common cause of death in CAH.[17]

Neuropsychiatric disorders are common in CAH patients. Adult patients with CAH are more likely to suffer from psychiatric disorders such as depression, anxiety, and adjustment disorders.[18] They may have suicidal tendencies or alcohol misuse.[19] Increased prevalence of injuries and accidents has also been seen in CAH patients, especially females.[20] Boyareddy *et al*.[12] have not reported neuropsychiatric manifestations in their patients. This area has not been well addressed in Indian studies and requires further investigations. Emotional perceptions may also be altered in youth with CAH, and these findings were associated with lower brain volumes in areas such as the prefrontal cortex, hippocampus, and amygdala.[21] Even in young children, especially girls, colour and toy preferences suggest effects of pre-natal androgen exposure of the brain.[22] Patients with CAH are at increased risk of osteoporosis, mainly due to life-long glucocorticoid therapy. The patients who are diagnosed late or have poor androgen control may have a better bone mineral density than those being treated early and optimally. Abnormal bone architecture has also been reported in CAH patients.[23] Older patients may be at higher risk of osteoporosis and fractures, but there are limited data in this respect. As found by Boyareddy *et al*.,[12] short stature has been frequently reported in CAH patients due to late diagnosis, exposure to gonadal steroids, and early puberty. Neonatal screening is essential in this regard. Apart from preventing other complications, neonatal screening has the potential to improve adult height. Data suggest that at least in male patients and those with simple virilising CAH, adult heights in those detected by neonatal screening were significantly higher than in those diagnosed prior to institution of neonatal screening programs.[24]

Considering the high prevalence of CAH in India, we need to establish robust neonatal screening programs, which can prevent many CAH-related mortalities and improve the outcomes of those who survive. We also need to be more cautious towards glucocorticoid therapy and treat cardiovascular risk factors aggressively in our patients. Widespread availability of genetic testing can help us understand the genetics of CAH in our population better and establish genotype–phenotype correlations for our patients. Indian Council of Medical Research has already performed a national task force study on CAH under the guidance from Government of India. A national level registry for CAH would be instrumental in generating more data and enabling further advances in this area. Last but not the least, we need to generate awareness among the general public and doctors regarding CAH so that deserving patients get the much needed specialised attention.

Address for correspondence: Dr. SV Madhu,
Department of Endocrinology, Centre for Diabetes, Endocrinology and Metabolism, University College of Medical Sciences and GTB Hospital, Delhi, India.
E-mail: drsvmadhu@gmail.com

References

1. ICMR Task Force on Inherited Metabolic Disorders. Newborn screening for congenital hypothyroidism and congenital adrenal hyperplasia. Indian J Pediatr 2018;85:935–40.
2. Berglund A, Ornstrup MJ, Lind-Holst M, Dunø M, Bækvad-Hansen M, Juul A, *et al.* Epidemiology and diagnostic trends of congenital adrenal hyperplasia in Denmark: A retrospective, population-based study. Lancet Reg Health Eur 2023;28:100598.
3. Ludwig K, Lai F, Wiley V, Ravine A, Srinivasan S. Genotyping in patients with congenital adrenal hyperplasia by sequencing of newborn bloodspot samples. J Pediatr Endocrinol Metab 2023;36:966–73.
4. Ravichandran L, Asha HS, Mathai S, Thomas N, Chapla A. Congenital adrenal hyperplasia-A comprehensive review of genetic studies on 21-hydroxylase deficiency from India. Indian J Endocrinol Metab 2024;28:117–28.
5. Tang P, Zhang J, Peng S, Wang Y, Li H, Wang Z, *et al.* Genotype-phenotype correlation in patients with 21-hydroxylase deficiency. Front Endocrinol (Lausanne) 2023;14:1095719.

6. Simpson JL, Rechitsky S. Prenatal genetic testing and treatment for congenital adrenal hyperplasia. Fertil Steril 2019;111:21–3.
7. Merke DP, Mallappa A, Arlt W, Brac de la Perriere A, Lindén Hirschberg A, Juul A, *et al.* Modified-release hydrocortisone in congenital adrenal hyperplasia. J Clin Endocrinol Metab 2021;106:e2063–77.
8. Rees DA, Merke DP, Arlt W, Brac De La Perriere A, Hirschberg AL, Juul A, *et al.* Comparison of modified-release hydrocortisone capsules versus prednisolone in the treatment of congenital adrenal hyperplasia. Endocr Connect 2024;13:e240150.
9. Auchus RJ, Hamidi O, Pivonello R, Bancos I, Russo G, Witchel SF, *et al.* Phase 3 trial of crinecerfont in adult congenital adrenal hyperplasia. N Engl J Med 2024;391:504-14.
10. Sarafoglou K, Kim MS, Lodish M, Felner EI, Martinerie L, Nokoff NJ, *et al.* Phase 3 trial of crinecerfont in pediatric congenital adrenal hyperplasia. N Engl J Med 2024;391:493-503.
11. Lin-Su K, Harbison MD, Lekarev O, Vogiatzi MG, New MI. Final adult height in children with congenital adrenal hyperplasia treated with growth hormone. J Clin Endocrinol Metab 2011;96:1710–7.
12. Boyareddy H, Kalra P, Dharmalingam M. Clinical and hormonal profile of classical 21-hydroxylase deficiency congenital adrenal hyperplasia: Experience from a tertiary centre in India. Indian J Endocrinol Metab 2023. doi: 10.4103/ijem.ijem_337_22.
13. Ridder LO, Balle CM, Skakkebæk A, Lind-Holst M, Nielsen MM, Hermann P, *et al.* Endocrine, cardiac and neuropsychological aspects of adult congenital adrenal hyperplasia. Clin Endocrinol (Oxf) 2024;100:515–26.
14. Falhammar H, Filipsson H, Holmdahl G, Janson P-O, Nordenskjöld A, Hagenfeldt K, *et al.* Metabolic profile and body composition in adult women with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Clin Endocrinol Metab 2007;92:110–6.
15. Chen L-M, Valentine A, Davis SM, Graber E, Fechner PY, Furniss A, *et al.* Multicenter analysis of cardiometabolic-related diagnoses in youth with congenital adrenal hyperplasia: A PEDSnet study. J Clin Endocrinol Metab 2024:dgae362. doi: 10.1210/clinem/dgae362.
16. Tamhane S, Rodriguez-Gutierrez R, Iqbal AM, Prokop LJ, Bancos I, Speiser PW, *et al.* Cardiovascular and metabolic outcomes in congenital adrenal hyperplasia: A Systematic review and meta-analysis. J Clin Endocrinol Metab 2018;103:4097–103.
17. Falhammar H, Frisén L, Norrby C, Hirschberg AL, Almqvist C, Nordenskjöld A, *et al.* Increased mortality in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Clin Endocrinol Metab 2014;99:E2715-21.
18. Engberg H, Butwicka A, Nordenström A, Hirschberg AL, Falhammar H, Lichtenstein P, *et al.* Congenital adrenal hyperplasia and risk for psychiatric disorders in girls and women born between 1915 and 2010: A total population study. Psychoneuroendocrinology 2015;60:195–205.
19. Falhammar H, Butwicka A, Landén M, Lichtenstein P, Nordenskjöld A, Nordenström A, *et al.* Increased psychiatric morbidity in men with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Clin Endocrinol Metab 2014;99:E554–60.
20. Falhammar H, Hirschberg AL, Nordenskjöld A, Larsson H, Nordenström A. Increased prevalence of accidents and injuries in congenital adrenal hyperplasia: A Population-based cohort study. J Clin Endocrinol Metab 2024;109:e1175–84.
21. Omary A, Khalifeh N, Cotter DL, Kim MS, Choudhury F, Ahmadi H, *et al.* Altered emotion perception linked to structural brain differences in youth with congenital adrenal hyperplasia. J Clin Endocrinol Metab 2023;108:e1134–46.
22. Neufeld SAS, Collaer ML, Spencer D, Pasterski V, Hindmarsh PC, Hughes IA, *et al.* Androgens and child behavior: Color and toy preferences in children with congenital adrenal hyperplasia (CAH). Horm Behav 2023;149:105310.
23. Sun X, Wu Y, Lu L, Xia W, Zhang L, Chen S, *et al.* Bone microarchitecture and volumetric mineral density assessed by HR-pQCT in patients with 21- and 17α-hydroxylase deficiency. Calcif Tissue Int 2023;113:515–25.
24. Hoyer-Kuhn H, Eckert AJ, Binder G, Bonfig W, Dübbers A, Riedl S, *et al.* Impact of newborn screening on adult height in patients with congenital adrenal hyperplasia (CAH). J Clin Endocrinol Metab 2023;108:e1199–204.

Access this article online

Quick Response Code:

Website: https://journals.lww.com/indjem/

DOI: 10.4103/ijem.ijem_333_24

How to cite this article: Raizada N, Madhu SV. Breakthroughs in congenital adrenal hyperplasia care - Hope on the horizon. Indian J Endocr Metab 2024;28:333-5.