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REVIEW

Childhood-onset growth hormone deficiency and the transition to adulthood: current perspective

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Abstract: Childhood-onset growth hormone deficiency (CO-GHD) is an endocrine condition associated with a broad range of health issues from childhood through to adulthood, which requires particular attention during the transition period from adolescence to young adulthood. There is uncertainty in the clinical practice of the management of CO-GHD during transition regarding the clinical assessment and management of individual patients during and after transition to obtain optimal follow-up and improved health outcomes. Despite the availability of clinical guidelines providing the framework for transition of young adults with CO-GHD, there remains substantial variation in approaching transitional care among pediatric and adult services. A well-structured and coordinated transitional plan with clear communication and direct collaboration between pediatric and adult health care to ensure optimal management of adolescents with CO-GHD during transition is needed.

Keywords: growth hormone deficiency, childhood-onset, transition, adolescents

Introduction

Transition is a planned process that aims to address the wider set of medical, psychological and educational requirements of young adults with chronic conditions as they move from pediatric to adult health services.[1] Increased survival of children with complex health conditions has led to growing attention on the importance of the quality of services provided for adolescents during transition. Childhood-onset growth hormone deficiency (CO-GHD) is one of a number of complex endocrine conditions that may have an impact throughout life, starting in childhood and continuing into adulthood. Transition of patients with CO-GHD that have been treated with recombinant human growth hormone (rhGH) during childhood is a challenging phase for health care providers. This phase occurs in CO-GHD from mid-late teens until approximately 6 or 7 years after final height has been reached.[2] This is a critical period for maximizing bone mass and muscle strength, which are important determinants for the risk of fractures related to osteoporosis occurring later in life.[3] The presented data largely support the positive role of rhGH therapy during the transition period of adolescence and beyond.[4,5] The effects of CO-GHD and the benefits of rhGH therapy during transition have been previously described in several studies.[6–10] Although there are numerous publications that have discussed transition in general with some specifically discussing CO-GHD,[2,6,11] a number of unanswered issues still remain.

Current practice during transition

Several clinical practice guidelines have described the theoretical framework for the transition of adolescents with CO-GHD.[2,12–15] However, in the clinical practice setting,

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both adult and pediatric endocrinologists lack consistency when managing the adolescent patients with CO-GHD during transition. The clinical experience in Scotland highlighted various areas of uncertainty in clinical practice:[16] the best method of evaluating the hypothalamic–pituitary axis, identification of patients to test, determining which test to use for diagnosing persistent growth hormone deficiency (GHD), identifying which patients would most benefit from continued rhGH treatment and methods of ascertaining if patients should continue treatment. In addition, it is unclear with whom the responsibility for the biochemical reevaluation of GHD lies, the pediatric endocrinologist or adult endocrinologist who will decide whether to continue rhGH therapy into adulthood and the involvement of patients and family in making the decision and management plan. Practice varies across the UK, particularly in cases when no organic cause for GHD is identified.[16–18]

The current guidelines classify CO-GHD according to the likelihood of persistent GHD.[2,12,13] A previous history of organic disease, deficits in two or more additional pituitary hormones,[19,20] hypothalamic–pituitary structural abnormalities as well as tumour-related organic GHD are strong predictors of persistent GHD.[21–24] Patients who are considered having a high probability of persistent GHD may not require their growth hormone (GH) status to be reevaluated and should continue rhGH without interruption. Those who are less likely to have persistent GHD should undergo reevaluation of the GH axis before resuming rhGH replacement therapy.[2] Although there are clearly stated criteria under both categories, other factors such as clinical observations and development of symptoms could influence the decision of how the patients are categorized and managed. In addition, there is no clear reevaluation pathway for those who exhibit a discordant GH and IGF-1 pattern.

The timing of retesting is another issue. According to guidelines, the decision when to reassess depends largely on attainment of adult height as defined (height velocity <2 cm/ year). The recommended washout interval between stopping rhGH and retesting is from 1 to 3 months,[2] although there are no existing data on the optimal shortest interval without rhGH for retesting reliability and health parameters. There is some evidence, however, that the longer interval and delay in reinstituting rhGH may have an impact on optimizing skeletal outcomes in these subjects,[25] as well as other parameters, such as cardiovascular and lipid profiles.[26] Moreover, a longer period off rhGH during reevaluation may increase the risk of losing patients to follow-up.[27]

GH stimulation tests are used to reevaluate GH levels taking into account the appropriate cutoff limits with various assay measurements.[28,29] The insulin tolerance test (ITT) is considered the gold standard to reevaluate secretion of GH in these patients. Assuming adequate hypoglycemia is achieved, this test can distinguish GH deficiency from the sufficient GH secretion that is linked with obesity and normal aging. This test, however, is contraindicated in patients with epilepsy or heart disease. Given this precaution, the only alternative reliable stimulation tests that can be used are glucagon/growth hormone-releasing hormone (GHRH)+arginine, taking into account appropriate cutoff limits.[2]

Cutoff levels for peak GH responses to stimulation tests during the transition period are still arbitrary; studies use a peak GH cutoff <5.1 µg/L,[23] <6.1 µg/L[30] or <5.6 µg/L.[31] The European Society for Pediatric Endocrinology recommended a cutoff <5 µg/L, using the ITT as an appropriate criterion for GH replacement during transition.[2] In CO-GHD where persistent GHD is highly likely, confirmation of persistent GHD can be made by a low IGF-I level alone (<−2 SD for age and gender) measured after at least 1 month off rhGH therapy, without the need for any further stimulation testing.[5] Figure 1 illustrates the current proposal workup of diagnosing and reevaluating CO-GHD patients during transition,[2] highlighting the areas of uncertainty.

It is currently recommended to restart rhGH at a low dose (0.2–0.3 mg/day) and then titrate to attain IGF-1 levels that fall into the upper half of the normal range. The dose of rhGH is then adjusted during the transition to adult treatment, with young females receiving oral estrogen requiring higher rhGH doses. IGF-1 should be measured during dose adjustment at 1–2-month intervals and also a minimum of once a year during therapy in order for it to be kept at an age- and sex-appropriate level.[2]

Benefits of rhGH during transition

The broader benefits of rhGH for optimizing other health aspects during childhood and the period of the transition to adulthood are becoming more widely recognized (Figure 2).[32,33]

Bone and fracture risk

There is currently conflicting evidence on whether CO-GHD contributes to low bone mass and an increased risk of fracture in adulthood,[34–36] although mechanisms and the pathophysiology of bone mass reduction are still far from fully understood. Indeed, many factors such as gender, height, age at onset, body composition, gonadal status, GHD severity and assessment methods may all contribute to inconsistent data on bone mass in patients with CO-GHD. Studies suggest that CO-GHD results in developmental bone mass deficits both at the time of diagnosis[37,38] and at retesting when final
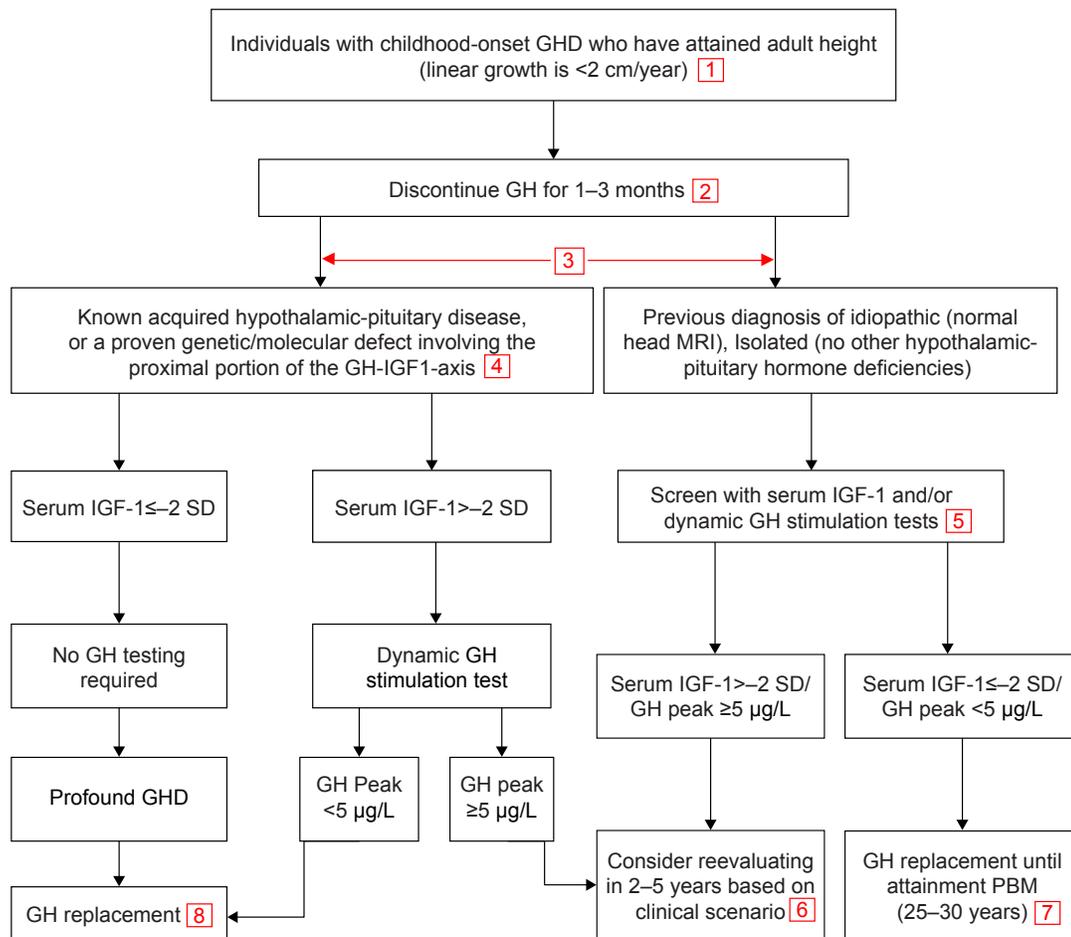
Figure 1 Schema for assessing the GH/IGF-1 axis during the transition period.
Notes: Areas of uncertainty: 1) who should have their GH axis reevaluated and who is responsible, pediatric or adult endocrinologist? 2) what is the optimal duration for washout? 3) what are the criteria for low and high risk of persistent GHD? 4) those with a high risk of persistence GHD, do they still require reevaluation or should they continue GH therapy? 5) what is the GH peak cutoff? 6) when and where to follow up those who no longer have GHD? 7) monitoring and the outcome of second reevaluation at age 25 and 8) what if patient declines GH therapy? Adapted with permission from the European Journal of Endocrinology, from Clayton PE, Cuneo RC, Juul A, Monson JP, Shalet SM, Tauber M. European Society of Paediatric Endocrinology. Consensus statement on the management of the GH-treated adolescent in the transition to adult care. *Eur J Endocrinol.* 2005;152(2):165–170. Copyright 2018. Permission conveyed through Copyright Clearance Center, Inc.[2]
Abbreviations: GH, growth hormone; GHD, growth hormone deficiency; MRI, magnetic resonance imaging; PBM, peak bone mass.

height has been reached.[39] Reinstitution of rhGH replacement beyond the attainment of final height in young adults who have persistent CO-GHD has been reported to have a positive effect on bone density with a net benefit change in bone mineral density (BMD) of lumber spine ranging from 3% to 6% after 1 year[35] or 2 years.[4,40–42] On the other hand, some studies did not find any change in BMD up to 2 years after either discontinuation of rhGH[43] or after reinstituting rhGH replacement therapy after final height has been reached.[34,44] In addition, there are scarce data on the link between bone density and fracture risk in adolescents and young adults with CO-GHD that were observed in adults with GHD and hypopituitarism.[45,46] Previous studies have reported increased fracture risk in adults with CO-GHD[47,48] and only in women with CO-GHD in another study,[49] while

another study did not find any difference in the risk of fracture in adolescents with CO-GHD compared with that in the normal population.[50] Therefore, there is no clear evidence that the CO-GHD results in low bone mass or increases the risk of fracture.

Body composition and muscle strength
During transition after withdrawal of childhood rhGH replacement therapy, several but not all studies have showed a significant decrease in lean mass (LM; −8%) parallel by increased fat mass (FM; 10%–17%) in patients with CO-GHD who were diagnosed with persistent GHD and had stopped rhGH for at least 2 years.[4,34,51,52] Restarting rhGH therapy resulted in a notable improvement in body composition, with LM increasing by 14% and FM being reduced by

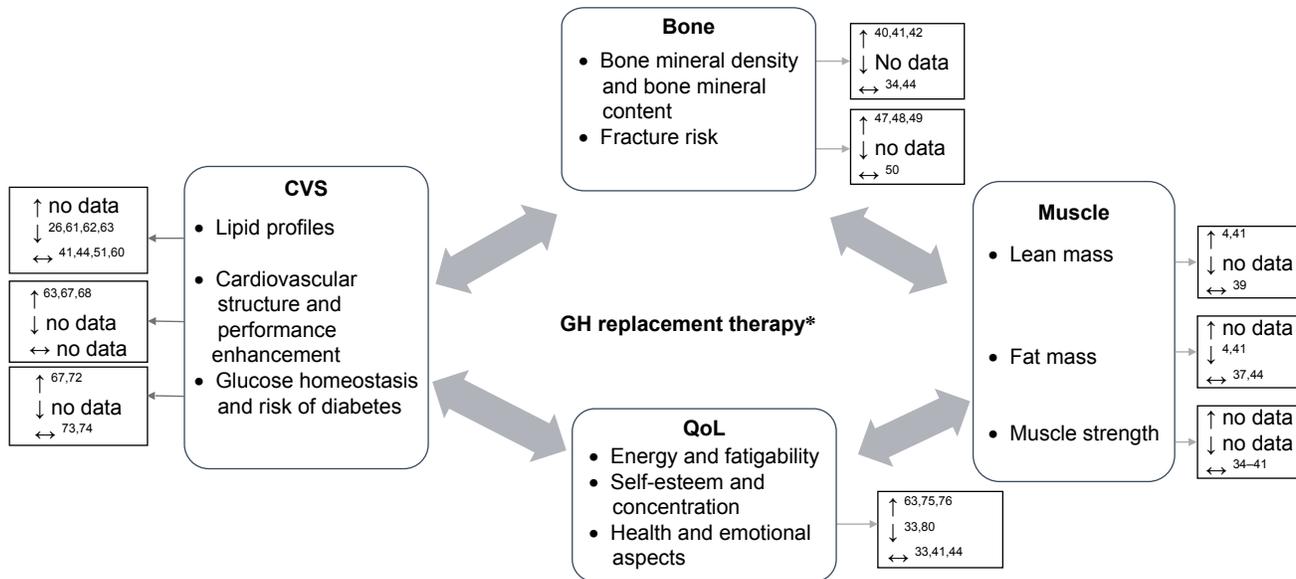**The impact of GH replacement therapy during transition of CO-GHD**

Bone
- Bone mineral density and bone mineral content
- Fracture risk

↑ 40,41,42
↓ No data
↔ 34,44

↑ 47,48,49
↓ no data
↔ 50

CVS
- Lipid profiles
- Cardiovascular structure and performance enhancement
- Glucose homeostasis and risk of diabetes

↑ no data
↓ 26,61,62,63
↔ 41,44,51,60

↑ 63,67,68
↓ No data
↔ no data

↑ 67,72
↓ No data
↔ 73,74

GH replacement therapy*

Muscle
- Lean mass
- Fat mass
- Muscle strength

↑ 4,41
↓ no data
↔ 39

↑ no data
↓ 4,41
↔ 37,44

↑ no data
↓ no data
↔ 34–41

QoL
- Energy and fatigability
- Self-esteem and concentration
- Health and emotional aspects

↑ 63,75,76
↓ 33,80
↔ 33,41,44

Figure 2 Impact of GH replacement therapy during transition of CO-GHD.
Notes: *Duration of GH replacement variable. ↑, increase; ↓, decrease and ↔, no significant changes or different.
Abbreviations: GH, growth hormone; CO-GHD, childhood-onset growth hormone deficiency; CVS, cardiovascular system; QoL, quality of life.

7% over 2 years of therapy.[4,41] In terms of muscle strength, previous studies have reported a lower maximum isotonic strength in young adults with CO-GHD, as measured by hand grip force,[53,54] but the effects on muscle strength in adolescents with CO-GHD during transition still remain to be completely elucidated.[55] There are some suggestions that reduced muscle mass was the cause of diminished muscle strength in GHD, as opposed to a reduction in contractile function.[56] Furthermore, it has been proposed that CO-GHD may initially result in a reduction in muscle mass and force, which would ultimately have an impact on bone density and geometry.[57] However, little research has been carried out into the relationship between muscle and bone strength in adult GHD patients,[58] and there has been no existing study targeting CO-GHD in children and adolescents.

Cardiovascular risks and glucose homeostasis

It has been reported in some studies that adolescents with CO-GHD have adverse lipid profiles after they discontinue rhGH treatment upon reaching final height,[26,51,52,59] but not all studies.[41,44,51,60] These parameters have been found to improve after restarting rhGH replacement therapy.[26,61–63] In addition, it has been noted that the longer the rhGH therapy is discontinued, the more abnormal the lipid profiles.[64]

It is possible that the alterations in lipid profiles observed when rhGH is discontinued may be partly explained by the short-term effects of rhGH therapy and therefore could not be analyzed independently of treatment duration during childhood.[65] Studies of adults with GHD provided evidence for this assumption, revealing that only long periods of rhGH therapy (in the range of 5–10 years) were associated with improved lipid profiles in adult GHD patients.[66,67] Further research is required to confirm this hypothesis in CO-GHD. In addition to aberrations in lipid profiles, direct impacts of CO-GHD on cardiac structure and function were reported in some echocardiographic studies. A study observed a decrease in all cardiac dimensions of adolescents with CO-GHD after withdrawal of rhGH during the transition period, when reinstituting rhGH results in a significant increase in left ventricular (LV) mass index and exercises capacity after 12–24 months[63,68] with improvement in endothelial function within the first 6 months of restarting rhGH.[69]

Regarding glucose homeostasis parameters, children with CO-GHD have been reported to be more insulin sensitive at the time of initial diagnosis[70] and after rhGH is withdrawn when they reach final height.[51,71] However, adults with GHD have been found to have an increased likelihood of insulin resistance,[67,72] but this is not the case for adolescents.[63] It is

not clear whether changes in glucose homeostasis in these subjects can be attributed to GHD itself, body composition and adiposity or both, with no clear evidence for an increased risk of developing diabetes.[73,74]

Quality of life (QoL)

GH/IGF-1 axis may play a role in normal brain structure, cognitive function, psychology and thereby QoL.[75,76] A study of children with isolated-GHD revealed a significant reduction in white matter, corpus callosum and neural volumes.[77] Given these findings, several clinical studies have been carried out to evaluate the effects of discontinuing and subsequently resuming rhGH treatment with regard to QoL elements in young adults with CO-GHD during transition from childhood to adulthood.

Some studies reported no changes in QoL in patients with CO-GHD, when measured at the time they discontinued rhGH after reaching final height and after 2 years remeasured while either off or resuming rhGH therapy.[33,41,44] Another study further reported no impairment in QoL in short-stature adolescents and children with GHD and without GHD,[78] which indicates that other unknown confounders could influence QoL other than height and GH levels.[79] On the other hand, other studies have stated that adolescent CO-GHD patients who had been treated with rhGH and then discontinued therapy after attaining height suffered from some cognitive and psychological impairment, particularly in domains of attention, memory, energy drive, emotional reactions and social isolation.[80,81] These measures significantly improved when rhGH treatment was restarted. An inverse relationship has been reported between QoL and rhGH therapy duration; a longer period without rhGH was associated with a poorer QoL, whereas restarting rhGH treatment had a significantly positive effect on health-related QoL aspects.[64] There is also some evidence that discontinuing rhGH treatment resulted in decreased QoL within 6 months, which was improved in 3–6 months after recommencing rhGH therapy.[81,82] Although individuals with GHD treated with rhGH reported having a higher self-esteem compared with short-stature and normal-stature children,[83,84] the replacement of rhGH in adult CO-GHD patients resulted in less QoL improvement than in those with adult-onset GHD,[33] even after undergoing rhGH therapy for long-term periods of 4–10 years.[85]

Challenges for future

The need for an appropriate transition service is increasingly recognized within health care systems. Generally, the purpose of transition is to offer adolescent patients continuity of care and promote mental and physical health through the exchange of information among health care workers in order to optimize their health and QoL aspects.[11] Although the existing guidelines have theoretically described how to reevaluate CO-GHD during transition, there is no clear pathway about how to organize and deliver transitional care from pediatric to adult services. Much of the transition literature has focused on the risk of untreated GHD during transition in terms of health and QoL outcomes; however, none of the studies have identified a clear transition plan, before and after reevaluation follow-up. Several studies have highlighted the risks of adolescents who drop out specialist endocrine care during the transition to adulthood care. The Scottish audit demonstrated 21% of patients stopped rhGH replacement without comprehensive reevaluation and 18% of patients did not attend follow-up while on treatment and never returned to endocrine clinics. This study has also highlighted issues about the follow-up of patients who no longer have GHD and particularly those patients with persistent GHD who have chosen not to resume adult rhGH treatment.[16] In another endocrine setting, transitional care was evaluated in patients with congenital adrenal hyperplasia reporting that 50% of the whole cohort were lost to follow-up following transfer to adult care,[86] with only 10% of the expected numbers still attending the adult endocrine service in another study.[87]

The current transition of endocrine conditions including GHD has been reported to be of suboptimal quality in young adults with endocrine conditions.[88,89] Such studies provide an insight into actual practice barriers and potential solutions for successful transition. The readiness of the patients and their caregivers, appropriate environmental setting and local resources were described as factors, which interfere with the precise format of the service and successful transition. There are various expert-based recommendations on how to improve transition and provide quality services for other chronic endocrine diseases, for example, type 1 diabetes mellitus,[90] turner syndrome,[91] and hypogonadism[92]. Other reports suggest some strategies for successful transition including standardized referral systems and establishment of transition centers to ensure that the needs of young adults with CO-GHD are being met.[93,94] In addition, for optimizing transitional care, it was recommended that pediatric and adult endocrinologists collaborate and share information while understanding that some overlap and a joint transition service would optimize the follow-up and transfer of

adolescents,[94] although there are lack of data about patient attendance and follow-up after transition. The existing theoretical generic models have demonstrated structured processes of transitioning adolescents from pediatric to adult care.[95,96] However, there appears to be clear difficulties in the feasibility of implementation of the all processes at every center and/or for every individual. Using the model designed by Gleeson et al, application of this model faces several challenges for effective transition of adolescents with CO-GHD as outlined in Table 1. In addition to the above highlighted areas of uncertainty in the schema of reevaluation and management of adolescents with CO-GHD, the model does not address issues concerning the readiness of patients and their caregiver to transition, transition clinic visits and frequency of appointments. The arrangement and duration to get the first adult care appointment, together with aspects to ensure the continuity of care, are also important factors. Therefore, there is a growing need to further review the current practices and develop more specific models for better planning and promoting the continuity of care during and after transition.

Conclusion

Transition is a concept of a multidisciplinary approach that ensures continuity of health care while adolescents with complex health conditions are transferred from pediatric care to adult care. There is some evidence that recommencing rhGH treatment in CO-GHD during transition results in not only improved growth and bone health but also a better prognosis for metabolic and cardiovascular risks in the long term. Further studies are required on the current practice of assessing and managing CO-GHD, as well as research into the long-term follow-up of patients who have been confirmed to have persistent CO-GHD and continuous monitoring for optimizing somatic and psychological outcomes in patients. The major challenge during this stage, however, is appropriately identifying candidates for adult GH therapy. The current guidelines need to be reviewed, addressing areas of uncertainly

Table 1 Transition process from pediatric to adult care

Generic model*		Application for CO-GHD	Challenges
Pediatric care	Young person and family work in partnership with health care professionals and have early discussions about transition planning	• Reassessment of etiology and disease-specific management • Reassessment of the GH treatment regimen • Assessment of readiness and preference of patients and their care giver	• Who, when, where and how to reevaluate GH axis • Referral to transition clinic
Transition care	Young person grows in knowledge, confidence and independence in managing their health care and other aspects of life	• MDT team include pediatric endocrinologist, adult endocrinologist, specialist nurses, access to psychologists and social workers • Discuss transfer plan • Family support – education and ability to self-manage • Restarting rhGH in those confirmed with persistent GHD • Clear plan for those who have GHD only patients to keep follow-up and reassessment in 2-years time	• Clinical resources • Patients and care giver need to be involved in the management • Transition clinic visit and frequency of appointments • Follow-up for those who no longer have GHD
Transfer	Young person is currently stable in terms of their condition and life, ready to transfer and demonstrates increasing autonomy in his or her health care	Plan first adult care appointment	• Arrangement and duration to get first adult care appointment • To ensure the continuity of care
Adult care	Young person is fully autonomous in health care and well on his or her way to achieving his or her adult potential	Full adult care	• Regular follow-up and rhGH replacement therapy • Monitoring health and QoL aspects
Follow-up		Reevaluation at completion of somatic growth (approximately 25–30 years)	• The outcome of reevaluation in young adulthood • Clinical decision

Note: *Model designed by Gleeson et al 2012.[88]
Abbreviations: CO-GHD, childhood-onset growth hormone deficiency; GH, growth hormone; MDT, multidisciplinary team; rhGH, recombinant human growth hormone; QoL, quality of life.

as evidenced by variation in clinical practice. Hence, clearly a structured transition protocol is a vital key to establish the best practice of transitioning adolescents with CO-GHD.

Disclosure

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