

REVIEW ARTICLE

Growth and puberty in children with HIV infection

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ABSTRACT. Children with perinatal HIV infection may present with clinical features of endocrine dysfunction such as growth failure and pubertal delay. Pediatric care providers and pediatric endocrinologists should implement appropriate preventive, screening, and therapeutic strategies to maximize survival and quality of life in these children. Growth and pubertal delay can be exacerbated by a variety of treatable infectious, endocrine, nutritional, and immunological disorders. Timely diagnosis and appropriate treatment of these conditions may lead to improvement or even normalization of growth and puberty. HIV-infected children with advanced disease should undergo periodic growth evaluation, including GH levels, IGF-I, IGF binding protein 3 and androgens, in order to identify subclinical endocrine dysfunction. However, little is known about the association between HIV infection and endocrine dysfunction in children. Highly active antiretroviral therapy may also be associated

with endocrine dysfunction with consequences on growth and puberty. Growth retardation and pubertal delay are always seen in children with advanced HIV infection and are often related to the proinflammatory milieu found in advanced AIDS. Growth and pubertal impairment are markers of advanced disease and require proper evaluation. A dysregulation of the hypothalamic-pituitary axis, toxic or allergic drug reactions may play a role in growth and pubertal delay of HIV-infected children. These dysfunctions require careful monitoring, in order to assess metabolic alterations that may be important in regulation of growth among HIV-infected children. Better understanding of the mechanisms leading to impairment of growth and puberty in children with perinatal HIV-1 infection might lead to appropriate treatment when required.

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INTRODUCTION

Pediatric HIV/AIDS is a leading cause of mortality and morbidity. In 2005, an estimated 2.3 million children were living with HIV, worldwide; 530,000 became newly infected and 380,000 died (1). Out of the total HIV-infected children worldwide, 63% are in Sub-Saharan Africa (1). It has been suggested that over 90% of the children living with HIV in Sub-Saharan Africa may have acquired the infection through mother-to-child transmission (2). According to UNAIDS (Joint United Nations programme on HIV/AIDS), about 1600 infants are born daily with HIV infection worldwide (1). However, the rates of maternal-to-child transmission of HIV vary by geographical location. In industrialised countries, pediatric HIV infection has largely been controlled. In these settings, HIV rates are less than 2%. In Africa, high rates of maternal HIV infection, high birth rates, inadequate access to available interventions, and prolonged breast-feeding increase the burden of pediatric HIV disease.

The transmission risk for a child born to an HIV-infected mother in an African setting without interventions for prevention of mother-to-child transmission is about 30-40% (3-5). The remaining 60-70% of children, although not HIV-infected, still have a 2- to 5-fold risk of mortality as a

direct consequence of the mother's HIV disease, when compared to children born to uninfected mothers. However, with the introduction of antiretroviral therapy, survival in HIV-infected children has significantly improved, making children more vulnerable to metabolic side effects of therapy (6). Infection with HIV is a multisystem process and may be anticipated to affect growth and metabolism. The extent and magnitude of the dysregulation of growth, pubertal development, and other endocrine functions correlates with the disease progression (7).

GROWTH

The growth pattern of children born to HIV-infected women is often impaired, particularly in Sub-Saharan Africa and other regions where the epidemic is taking the highest toll and access to antiretroviral medications are limited (8-10). Numerous studies have shown that HIV infected infants born to HIV-positive mothers are usually shorter and thinner than uninfected but HIV-exposed infants or infants born to uninfected mothers (11-13), and have a smaller head circumference (14). Linear and ponderal growth retardation is severe in children who become infected (15, 16) as early as 3 months after birth (17), however the birth weight is not significantly affected due to the fact that the highest transmission take place near/during delivery (18, 19). The cause of this HIV-related growth failure is complex (20-24). These include alterations in gastrointestinal function, chronic/recurrent infections, and endocrine dysfunction. Although causes of HIV-associated growth retardation are

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not completely understood, a role of GH dysfunction has been suggested (16).

Children differ from adults in such a way that they tend toward developmental retardation and failure of somatic growth (25-30) with occasional immunosuppression (31). Deficiencies in GH and IGF-I levels have been seen at all clinical and immunological stages of disease, but are most pronounced in advanced cases (32). Early HIV infection therefore may cause endocrine dysfunction characterized by dysregulated GH secretion. Decreased GH secretion has been reported in children not on treatment, but primary GH deficiency has been identified only occasionally (33). The circadian secretory pattern of GH and stimulated GH levels are normal in the great majority of children with HIV infection (34, 35). Because of the episodic pattern of GH secretion, incidental GH concentration measurements provide inadequate information about the amount of GH secreted over a longer period. Similarly, IGF-I has variably been reported as normal (34) or reduced (35). In children with wasting syndrome and/or active disease, acquired GH resistance is seen, with increased GH levels and decreased concentrations of IGF-I (36). Therefore, the expected GH-induced increase in IGF binding protein 3 (IGFBP-3) is blunted (37). On the other hand Frost et al. (38), suggested an enhanced proteolysis of IGFBP-3 to be associated with failure to thrive. In experimental studies, the infusion of HIV glycoprotein 120 (gp120) into the rat brain caused release of interleukin 1 or tumor necrosis factor (21), which suppressed GH and GHRH at high concentration (22). Furthermore, the envelope protein gp120 at its low concentration causes death of neurons by indirect mechanisms (23, 39, 40), on top of slowing/preventing the appearance of developmental milestones in neonatal rats (41). A similar mechanism could be taking place in HIV-infected children. Furthermore, there is a close sequence homology between a 5-amino acid epitope of GHRH [the homologous peptides vasoactive intestinal peptides (VIP) and signaling molecule (PACAP)] and peptides derived from the V2 region of the gp120 molecule (42), which suggests that gp120 could compete for GHRH and VIP receptors, potentially contributing to GH suppression. A recent study (43) demonstrated that the gp120 antagonist D-Ala-Pep-Tide-T-Amide (DAPTA), when co-administered with gp120, is able to prevent the GH suppression, suggesting that the effects of gp120 at the level of the hypothalamus may occur through suppression of VIP receptor-mediated GHRH release. Because VIP can stimulate GHRH release from the hypothalamus (39), it is also possible that gp120 blockade of GHRH and/or VIP on their pituitary receptors could further inhibit secretion of GH, hence poor growth.

There is also an association between GH concentration and lipodystrophy (36, 43-52), in patients receiving highly active antiretroviral therapy (HAART). On the contrary, normal GH secretion has been reported in otherwise healthy HIV-infected patients, without demonstrated wasting or lipodystrophy (53). Although the mechanisms of these changes in fat redistribution have not been elucidated, recent data suggest a strong inverse correlation between increased visceral fat and reduced GH concentrations (54). The HAART-associated lipodystrophy syn-

drome has not been extensively studied in children, but it occurs more often than thought, although the manifestation is less severe than in adults (55-61). The entire spectrum of morphologic and metabolic derangements reported in adults has also been described in HIV-infected children and adolescents (55, 57, 59, 62). It has been shown that recombinant human GH (rhGH) therapy reduces the abdominal and dorsocervical fat in addition to improving lipid profile and lean mass in HIV-infected adults with abnormal fat accumulation (63-65). These changes are related to an overall satisfactory increase of IGF-I which may improve in children. These facts give an initial proof that the use of rhGH may be an advantageous treatment strategy for pediatric lipodystrophy. GH treatment has a lipolytic action; however the duration of HAART can contribute to peripheral lipodystrophy as described in HIV-infected children (61, 62).

A study performed on adult patients using GHRH showed a reduction of visceral adipose tissue (VAT), a significant reduction in VAT/subcutaneous adipose tissue (SAT) ratio during treatment, and no worsening of peripheral lipodystrophy (29). Additionally, no substantial changes in GH secretion were observed during the trial with GHRH. These results may suggest that GHRH supplements could be efficient to accomplish VAT reduction without a reduction in SAT. Further studies are therefore necessary in HIV-infected children for a clear picture on the risk/benefit of rhGH therapy in pediatric lipodystrophy.

Protein malnutrition, one of the features of HIV-infected children, is linked to combined GH and IGF-I resistance. In addition, serum IGF-I levels are low despite IGF-I resistance. This obvious paradox may arise directly from contemporaneous GH resistance or result from the ability of undernutrition to overrule an increased serum IGF-I level, which might be predicted based on standard negative feedback, as usually occurs with ligand when there is reduction of receptor activity and/or reduction in downstream post receptor function. Resistance to GH, IGF-I, and other growth factors have been suggested as a potential cause for growth failure in children with pediatric HIV-1 infection (66, 67). Both normal and low serum IGF-I levels have been described in HIV-1-infected children and adults; however the effect is more pronounced in children with failure to thrive (FTT). Additionally, low levels of IGFBP-3 and acid-labile subunit, members of the circulating ternary complex, have been reported to be low in poorly growing children with HIV-1 infection; and these children tend to have increased IGFBP-3 proteolysis, as seen in other hypercatabolic states (38). The mechanism by which IGF-I resistance develops in children with symptomatic HIV-1 infection could be linked to the augmented production of cytokines which occurs in patients with AIDS. If the mechanism for the GH and IGF-I resistance in children with symptomatic HIV-1 infection involves the IGF-I receptors (IGF-IR), one might also anticipate resistance to supraphysiological concentrations of insulin, the action which is normally mediated through the IGF-IR (34). Existence of circulating inhibitors of IGF-I action may possibly explain resistance to GH and IGF-I without resistance to supraphysiological concentrations of insulin, one of the mechanisms being increased production of IGFBP (68).

Another concern is the occurrence of an excessive accumulation of intra-abdominal adipose tissue (IAT) in HIV-infected children with overt signs of lipodystrophy and this is associated with longer duration of HAART (62). The optimism generated by overall improving health among patients on HAART has been tempered by concerns that these therapies may be associated with adverse metabolic effects, such as insulin resistance, hyperlipidemia, and changes in body composition (69-74). Veldhuis et al. (75) demonstrated that the degree of body fat was associated inversely with indices of GH secretion and free fat acids (FFA) remained negatively associated with peak GH response to GHRH. Similarly, GH response to GHRH has been improved in patients using acipimox, suggesting that FFA may play an inhibitory role with respect to GH secretion in the HIV lipodystrophy (76). Furthermore, FFA has been found to increase in the lipodystrophic patients, with increased GH response to GHRH in relation to decrease in FFA after acipimox administration (76). This suggests that increased FFA inhibits GH response to GHRH in lipodystrophic patients. Previous studies (52, 77, 78) in HIV-lipodystrophic patients with visceral adiposity demonstrate increased FFA and lipolysis rates. Changes in fat redistribution may occur due to HIV itself or exposure to HAART. There are different mechanisms leading to decreased GH, insulin resistance, and increased FFA in these patients: some of the mechanisms include somatostatin tone, reduced GH response to GHRH, and decreased ghrelin. Consequently, decreased GH may contribute to visceral adiposity and insulin resistance (79), creating a vicious cycle of metabolic dysregulation. Additionally, altered GHRH pulsatility or GH responsivity to GHRH at the pituitary lead to a decrease in GH release. A number of studies (75, 80, 81) have suggested that the mechanism by which the increased amounts of FFA may cause blunted GH secretion is by increasing endogenous somatostatin tone. However, studies performed in animals suggest that FFA impaired GH release directly at the pituitary gland (82). It is likely that excess FFA may alter GH secretion in severe lipoatrophy without visceral adiposity. Another mechanism for the reduction of GH release in HIV-infected patients is reduced ghrelin (76). In adult HIV-infected patients with lipodystrophy ghrelin is reduced and this was associated with reduced mean GH pulse, GH secretion, and increased insulin, suggesting that increased somatostatin and excess FFA impair GH response to GHRH. GH reduction is also seen in obese non-HIV-infected patients, as well as reduction of GH indices (75, 79, 80). HIV lipodystrophy on the other hand is unique, in those patients without severe generalized obesity, but displays fat redistribution, in such a way that total fat is not increased. Visceral adiposity is a significant predictor of GH deficiency/resistance in HIV-infected patients. IGFBP-3 proteolytic activity is a beneficial response to stress/injury (83, 84), hence reduction of IGFBP-3 affinity to IGF-I conserves a positive nitrogen balance on the expense of growth in HIV infected children. Thus the proteolysis of IGFBP-3 has a direct impact on linear growth of HIV-infected children.

These studies suggest a complex representation whereby alterations in insulin and fatty acids affect GH secretion in HIV-lipodystrophy, a phenomenon which may apply

to children and impair growth. Thus, GH has important effects on fat metabolism in both childhood and adulthood and GH replacement may lessen health risks associated with increased adiposity. Some studies (32, 85, 86) have shown weight gains with rhGH, plus recombinant human IGF-I or GH only administration. rhGH reduces excess accumulation of IAT in lipodystrophic HIV-infected adults, while data in pediatric patients is still scarce; Viganò et al. (87) showed that rhGH in HIV-infected adolescents reduces IAT, trunk, and also limb fat, while increasing lean mass. Overall short-term rhGH is well tolerated and is not associated with worsening of glucose and lipid metabolism, but data are lacking on chronic use of GH in children. The evidence that GH levels are suppressed with HIV-1 infection together with reports that exogenous GH ameliorates AIDS-associated wasting suggest that HIV infection or viral proteins disrupt endocrine function, leading to diminished GH production, which in turn contribute to growth impairment in children.

In summary, the growth promoting agents that can be effective in HIV-infected children should have inhibitory factors on IGFBP-3 proteolysis and be able to increase the concentration of IGF-I. Similarly, drugs that block the GH suppressing actions of gp120 like DAPTA should be considered for their potential therapeutic efficacy by their ability to normalize endogenous GH levels.

PUBERTAL DEVELOPMENT

Virtually all children with chronic illnesses present with delayed puberty, which is associated with delayed growth and pubertal growth spurt. The earlier the onset and severity of disease, the greater the negative effect on pubertal growth. In HIV-infected children, delay in the onset of pubertal delay is the result of GH dysregulation, hypothyroidism, and testosterone reduction (88). Also, HIV infection has been associated with hypothalamic-pituitary-gonadal (HPG) dysfunction (30, 89).

The HPG axis is profoundly affected in caloric protein energy malnutrition which is a feature of HIV-infection, hence reduced growth with consequent delayed puberty (89). Malnutrition inhibits gonadotropin secretion, probably via an effect on LHRH neurones (90) which can result in gonadotropin deficiency.

The pubertal delay relates both to the infection itself and HAART, consequently children show height-weight and pubertal retardation. A longitudinal study in transfusion-infected boys found that age-adjusted testosterone levels decreased with decreasing immune function and, subsequently, delayed pubertal development and growth failure (91). Adolescents may be particularly vulnerable to hormonal changes because the HPG axis has not yet fully matured.

Delayed puberty is more pronounced in females than males (92), probably due to the difference in the sensitivity of pituitary to GnRH. FSH and LH levels are low or normal, suggesting a central component of the hypogonadism (93). In advanced disease, testosterone levels are low as a result of both gonadal and extragonadal factors that contribute to testicular dysfunction (94, 95). An increment of plasma HIV RNA has been associated with decrease in testosterone level, an effect which is more

pronounced in those children with high number of viral load and decrease in CD4+ count.

Different studies (27, 92, 96) have shown that children with perinatal HIV infection have delayed puberty associated with the severity of the disease. Part of the linear growth failure could be attributed to the delay in puberty. The hemophilic growth and developmental study investigated the relationship between HIV-associated immune dysfunction and puberty; their findings showed a significant delay in pubertal development associated with increasing levels of immune dysfunction (91).

The euthyroid sick syndrome accompanied by increased basal TSH levels, FT₄ levels, low IGF-I and IGFBP-3, due to proinflammatory interleukin production triggered by HIV-1 may be the mechanism leading to delayed sexual maturation.

CONCLUSION

A dysregulation of the hypothalamic-pituitary axis, toxic or allergic drug reactions may play a role in endocrine dysfunction in HIV infected children. These dysfunctions require an endocrine function monitoring, since they have relevant effects on growth and pubertal development. A better understanding of the mechanisms leading to growth impairment and delayed puberty in children with perinatally acquired HIV-1 infection might lead to appropriate treatment when required. There is a need for deeper knowledge on the mechanisms leading to delayed puberty which could direct development promoting strategies. Further studies are warranted to investigate the mechanisms leading to delayed puberty.

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