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CONSENSUS STATEMENT

Growth hormone treatment of adolescents with growth hormone deficiency (GHD) during the transition period: results of a survey among adult and paediatric endocrinologists from Italy. Endorsed by SIEDP/ISPED, AME, SIE, SIMA

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Abstract Treatment of adolescents with growth hormone deficiency (GHD) during the transition period is a controversial issue. This paper is a contribution from the Italian community of paediatric and adult endocrinologists surveyed in a Delphi panel. The Delphi method is a structured communication technique, originally developed as a systematic, interactive forecasting method that relies on a panel of experts. The experts answer questionnaires in two or more rounds. There was substantial agreement on the definition of the problems associated with the diagnosis and treatment of adolescents with GHD in the transition period, as well as on the identification of the controversial issues which need further studies. There is general consensus on the need of re-testing all isolated idiopathic GHD after at least 30-day withdrawn from treatment, while in patients with multiple pituitary deficiency and low IGF-I levels there is generally no need to re-test. In patients with permanent or confirmed GHD, a starting low rhGH dose (0.01–0.03 mg per day) to be adjusted according to IGF-I concentrations is also widely accepted. For those continuing treatment, the optimal therapeutic schedule to obtain full somatic maturation, normalization of body composition

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and bone density, cardiovascular function and Quality of Life, need to be evaluated.

Introduction

There is general agreement that GH treatment should be continued in patients with permanent growth hormone deficiency (GHD) during the transition period between late puberty and complete psychophysical maturity (between 15 and 25 years) after attainment of adult height [1]. These patients may in fact present body composition and metabolic abnormalities related to their GHD as well as to other pituitary hormone deficiencies. Discontinuation of treatment may lead to deterioration of metabolic profiles and reduction of bone mass [2–8]. However, there is still much controversy regarding a number of issues. The definition of the transition period [3, 9, 10] is a relatively new concept and many physicians are not familiar with. The need to continue treatment, when and how to re-test, as well as the GH cut-off values to confirm the diagnosis of GHD is not well defined [11–14]. Furthermore, the dose of GH administration, how to monitor adherence to treatment, and its efficacy during the transition period, as related to both metabolic and body composition parameters, and Quality of Life (QoL) are still questioned [15–17]. In this regard it should be pointed out that the impact of GH replacement during the transition period has not been adequately assessed in randomised clinical trials. Furthermore, no validated questionnaires are available to assess QoL in patients on GH replacement in the transition period.

Another important issue is related to the definition of who should be in charge for the management of the patient in the transition period, whether this requires a multidisciplinary approach or not [18], and how this multidisciplinary approach would be defined and streamlined.

Current guidelines do not solve all the aforementioned controversial issues [3, 18–22]. This survey was carried out to investigate the current approach to the patient with GHD during the transition period among a number of Italian adult and paediatric endocrinologists.

Methods

Sixteen adult and paediatric endocrinologists from Italy were surveyed in a Delphi panel. The Delphi method is a structured communication technique, originally developed as a systematic, interactive forecasting method that relies on a panel of experts (Fig. 1). The experts answer questionnaires in two or more rounds. After each round, a facilitator provides an anonymous summary of the experts' forecasts from the previous round as well as the reasons they provided for their judgments. Thus, experts are encouraged to revise their earlier answers in light of the replies of other members of their panel. It is believed that during this process the range of the answers will decrease and the group will converge towards the "correct" answer [23, 24].

The Delphi methodology was chosen because it is a well-tested method for this type of process, and was applied according to a web-based approach designed to promote participation and a focus on quality (introduction of the issues to be addressed without constraints). A flow chart describing the process is illustrated in Fig. 1. The addressed issues included a definition of the transition period and diagnosis of GHD, withdrawal of treatment and re-testing, modalities of treatment, effects of treatment. The process was carried out in three stages, the first two on an individual basis and the third based on discussion and sharing of opinions between participants.

Results

There was substantial agreement on the definition of the problems associated with the diagnosis and treatment of adolescents with GHD in the transition period, as well as the identification of the controversial and still less understood issues which need further studies (see Table 1).

Definition of transition

The transition period refers to physical and psychosocial changes, defined as starting in the late of puberty and ending with full complete maturation (3). This implies a "tempo" from mid to late teens until 6–7 years after the attainment of final height. Consequently, it is inappropriate to consider this phase as an extension of adolescence or an early aspect of adulthood [1].

Diagnosis

There is agreement that more research is needed on the diagnosis and treatment of GHD during the transition period focused to a better definition of diagnostic cut-offs for the GH levels [1, 3, 11, 19]. Furthermore, there is no clear-cut definition of less severe GHD deficiency, which is only taken into account in some conditions (e.g.,

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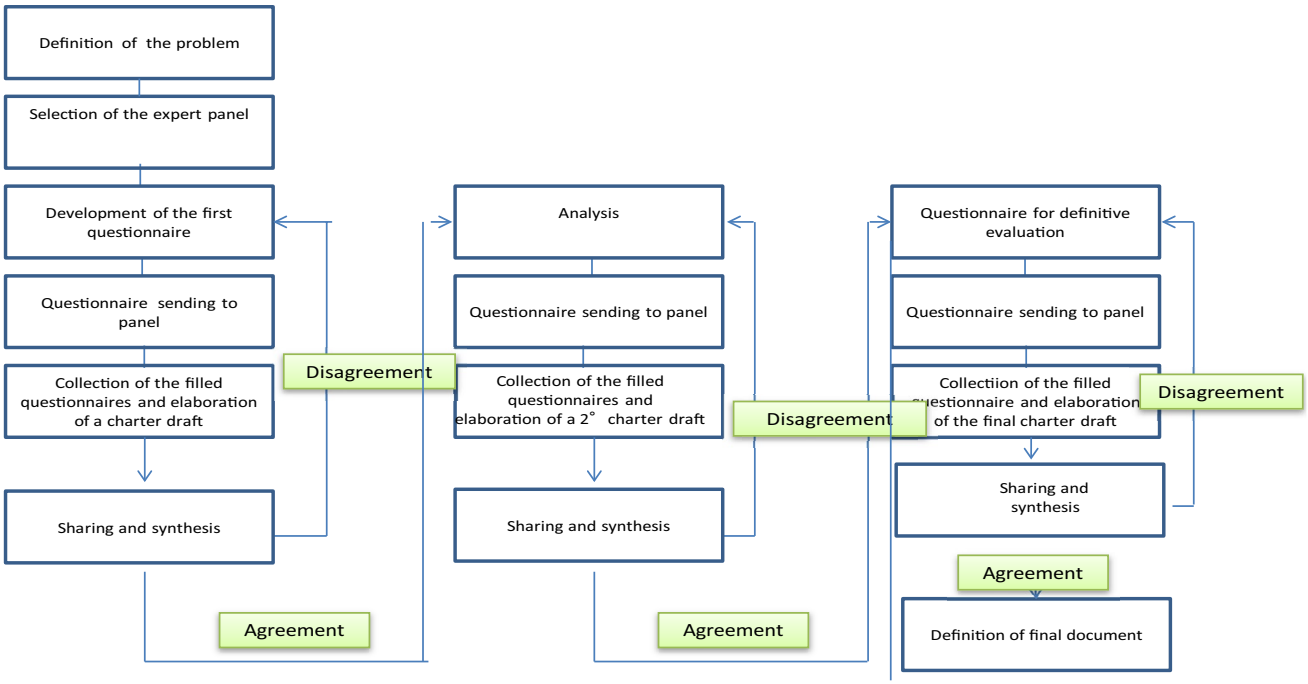

Fig. 1 The Delphi process. The first two stages were carried out on an individual basis and the third with the definition of the final document was based on a general discussion and sharing of opinions between participants

Table 1 Summary of the levels of agreement

Substantial agreement	Partial agreement	Agreement for future studies
Diagnosis, time of re-testing, re-testing modalities	Partial agreement between current practices and recommendations	Need to produce shared guidelines
GH dose, withdrawal from treatment	Definition of partial GH deficiency	Questionnaire on QoL at the transition age, validated for Italy and Europe
	Identification of biochemical criteria to diagnose GHD during the transition period	Definition of transition period and GHD
	Monitoring of treatment by a multidisciplinary team led by an endocrinologist	Definition of non severe GHD (problems related to IGF-I assay and need to standardize)

post-operative status, irradiation, etc.), as well as on the effect of treatment. In these patients there is also general agreement that GHD should be confirmed by re-testing after withdrawn of treatment for 30 days at least. Longer intervals may be needed for reassessment of particular cases, due to the presence of other conditions and the ensuing need to verify the reversibility of some abnormalities (involving the heart, the bones, etc.). The preferred stimulation tests are ITT and GHRH + Arg. The currently accepted cut-off value for ITT is 6.1 μg/l (96 % sensitivity and 100 % specificity), and it is recognized that ITT may cause severe hypoglycaemia and is contraindicated in patients with cardiac, neurological and adrenal diseases [25–28]. The currently accepted cut-off value for GHRH + Arg test is 19 μg/l (100 % sensitivity and 97 % specificity) [13]. Side effects are minor, but the test has poor reproducibility and is not useful in patients with hypothalamic abnormalities (including irradiated patients). The GH response to this test is also markedly affected by the BMI, making it less useful in obese or overweight subjects [13, 29]. The glucagon test is used in some centres, although it has never been validated in the transition period [30, 31].

According to current guidelines (3) and to the Italian Medicine Agency (AIFA), re-testing should not be performed in patients with genetically GH deficiency (mutations of the GH and GHRH genes) or multiple pituitary deficiencies with at least three hormonal deficits [idiopathic deficiency, genetic deficiency or deficiency associated with hypothalamic-pituitary abnormalities and IGF-I levels <−2 standard deviation (SD) scores]. Some recommendations of current guidelines, not yet implemented by AIFA, should be considered, including the combined presence of a low IGF-I level and evaluation of the clinical context and of the

risk/benefit ratio [32, 33]. In this regard it is recognized that treatment should result in IGF1 values of between 0 and +2 SD, even though current assays are not entirely reliable [34]. Furthermore, evidence of deterioration of the metabolic profile (lipid abnormalities), muscle mass and bone mass (by DEXA) and cardiac performance (Ultrasound evaluation of cardiac size and function) in untreated subjects should also be carefully taken into consideration [35–38].

Treatment

Treatment should be re-instituted in patients with confirmed GHD. The dose of GH should be tailored and titrated against IGF-I concentrations. The starting dose should be about half the dose recommended for children (0.01–0.03 mg/kg/day), but higher doses are used in some centres, and should be adjusted bimonthly based on IGF-I concentrations, which should be maintained between 0 and 2 SDS [3, 39–41]. The dose should be lowered or treatment should be discontinued in case of side effects such as arthralgia, headache, hyperglycaemia. According to the current evidence and guidelines, in female patients on oestrogen replacement therapy, the GH dose need to be augmented or lowered depending on the route of oestrogen administration, i.e. oral or transdermal route [3, 42, 43].

Monitoring

Blood pressure, weight and waist circumference, lipid profile, IGF-I levels, serum glucose and HbA1c should be monitored every 6 months. Bone mineral density by DEXA, intima media thickness, specific QoL questionnaires should be evaluated every other year [44–50]. Besides IGF-I levels, the patient's medical conditions, the level of adherence to treatment, as well as various factors, including BMI, gender and other replacement therapies, should also guide in dose adjustment. In patients with additional pituitary hormone deficiencies, other parameters should be monitored related to the specific defects. These parameters include thyroid hormone measurement, serum electrolytes, and serum and urine osmolarity. It is expected that GH and other pituitary hormone replacement result in amelioration of biochemical, hormonal and body composition parameters.

It is recognized that the effects of GH treatment differ as a function of age and medical history of a patient with severe GHD. In young people with childhood onset GHD treatment aims at preventing alterations in muscle and bone function and in lipid profile. In subjects diagnosed in the transition period, replacement therapy aims at normalising the alterations that may already be present [39, 46, 49].

There is a general agreement that GH improves bone mass and bone metabolism, body composition, muscle strength and performance, intermediate metabolism, cardiac and cardiovascular functions, and reproductive axis functioning, with positive effects on fertility [39, 46, 49, 51, 52].

It is also recognized that all metabolic and body composition abnormalities may be due to GHD as well as to other pituitary hormone deficiencies. Therefore, attention to correct replacement therapy of all hormonal deficits is mandatory to obtain the expected benefits. Furthermore, careful reassessment of pituitary function at the end of the transition period is also needed.

Conclusions

This survey was carried out to investigate the current attitude of adult and paediatric endocrinologists from Italy on growth hormone treatment of adolescents with GHD during the transition period. The period from the adolescence through early adulthood is characterized by physical and psychological changes. Treatment is aimed at correcting the GHD-associated abnormalities including reduced bone mineral density, muscle strength, lipid profile, glucose metabolism and serum IGF-I levels. The results show that there is general consensus on the need of re-testing all isolated idiopathic GHD after at least 30-day withdrawn period. In patients with multiple pituitary deficiency and low IGF-I levels there is generally no need to re-test, since it has been repeatedly shown that these patients have permanent GHD [30].

There was no general agreement on the existence/definition of partial (or less severe) GHD in the transition period. Also there was no general agreement on the need to continue treatment in adulthood in the absence of QoL data. The GH values of 6.1 and 19 μg/l after ITT and GHRH + Arginine, respectively, seem, up to date, the best cut-off limits although with some limitations linked to the effect of BMI on GH secretion and to the origin (pituitary or hypothalamic) of the defect. It is also widely accepted that GH treatment should be initiated with a low dose (0.2–0.5 mg per day) to be adjusted according to IGF-I concentrations. For those continuing treatment, the optimal therapeutic schedule to obtain full somatic maturation, normalization of body composition and bone density, cardiovascular function and QoL, need to be carefully evaluated. General agreement has been reached on the need to continue research on the effect of treatment on body composition, bone metabolism, intermediate metabolism, and QoL.

In conclusion, this Delphi-based survey has allowed to confirm that Italian paediatric and adult endocrinologists do follow current guidelines in the diagnosis and treatment

of GHD patients in the transition period. The discussion did not bring to attention issues not previously considered in the literature, nor the need to adapt the current recommendations to particular conditions.

Conflict of interest The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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