Idiopathic Short Stature

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Idiopathic short stature (ISS) can be subcategorized into familial and non-familial ISS and both can be associated with normal or delayed puberty. ISS is a diagnosis of exclusion, so that a thorough medical and physical examination and additional investigations should be performed, sometimes followed by genetic tests (1). In the last decades, several novel genetic syndromes were discovered which initially were considered ISS, for example mixed gonadal dysgenesis (45,X/46,XY) (2) and mutations in *GHR, IGFALS* (3), *SHOX* (4) and *NPR2* (5). Two extensive reviews (6,7) formed the basis of an international consensus meeting on ISS, where virtually all issues related to ISS were discussed (8).

ISS is not a registered indication for growth hormone (GH) treatment in Europe, but it is in the USA and various other countries. The basis for the indication were a randomized controlled study from the USA (9) and a European dose-response study (10), showing that GH leads to a 3-7 cm adult height gain. One of the reasons for non-acceptance by the European authorities is that most short children function normally and in most studies, no significant decrease of health-related quality of life could be documented. However, in some short children stress exposure is elevated, particularly by being teased (7).

An alternative therapeutic approach is to delay or diminish the effect of sex steroids, particularly estrogens, through gonadotropin-releasing hormone (GnRH) analogues or aromatase inhibitors. GnRH analogues alone are little effective if pubertal onset is within the normal range. The combination of GnRH analogues with GH for 3 years leads to 5 cm adult height gain and seems more efficacious in girls compared to boys (11). Anabolic steroids, such as oxandrolone, increase height standard deviation score in childhood, but do not change adult height (7). Finally, one can also consider psychological counseling.

For all potential medical interventions one should realize that more data on safety (particularly on the very long term) are needed (12). Ethical and health economic considerations are also relevant with regard to treating children with ISS [reviewed in (7)].

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