Time trends in age, growth hormone dose and height standard deviation score at treatment start (2006–2014) in short children with growth hormone deficiency, born small for gestational age and with Ullrich–Turner syndrome enrolled in NordiNet® International Outcome Study in Germany and the Czech Republic

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MŠ is a member of NordiNet® IOS International Study Committee. EP, SM-F and BTP are employees of Novo Nordisk.

Introduction

- Early diagnosis and timely initiation of growth hormone (GH) treatment are key to ensuring optimal clinical outcomes for children with short stature.[1]
- However, diagnosis and treatment of short stature are frequently delayed and consequently clinical outcomes may be suboptimal.[2]
- Furthermore, there is often an imbalance between genders with a bias towards more boys than girls being diagnosed and treated.[3,4]

Aims and Objectives

- To analyse time trends in baseline parameters at start of GH treatment from 2006 to 2014 in short children with GH deficiency (GHD), born small for gestational age (SGA) and Ullrich–Turner syndrome (TS) from Germany and the Czech Republic enrolled in NordiNet® International Outcome Study (IOS).

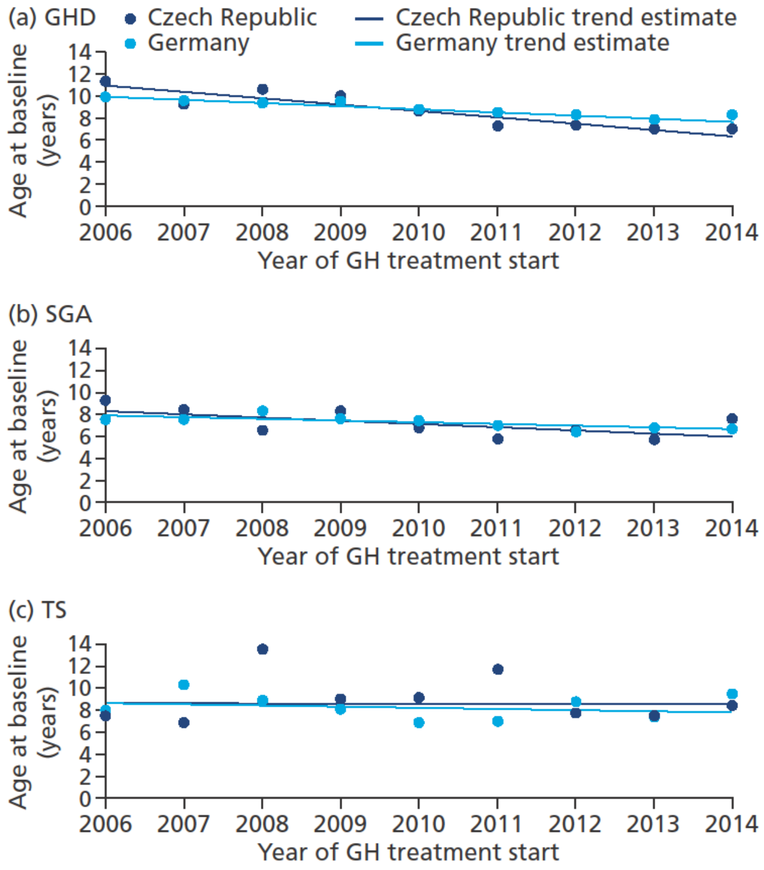
Methods

- NordiNet® IOS (NCT00960128) is a non-interventional, multinational study evaluating the long-term effectiveness and safety of GH (Norditropin® [somatropin; recombinant GH], Novo Nordisk A/S, Denmark) in a real-life clinical setting.[5]
- Time trends in baseline data (body mass index [BMI], chronological age, GH dose, height) from paediatric patients (<18 years) enrolled in NordiNet® IOS in Germany and the Czech Republic who started treatment with GH between 2006 and 2014 were analysed using a multiple regression model including country and year. Regression plots were used to illustrate trends in the data.
- Standard deviation scores (SDS) for height and for BMI were calculated using national[6,7] and World Health Organization (WHO)[8,9] references, respectively.

Results

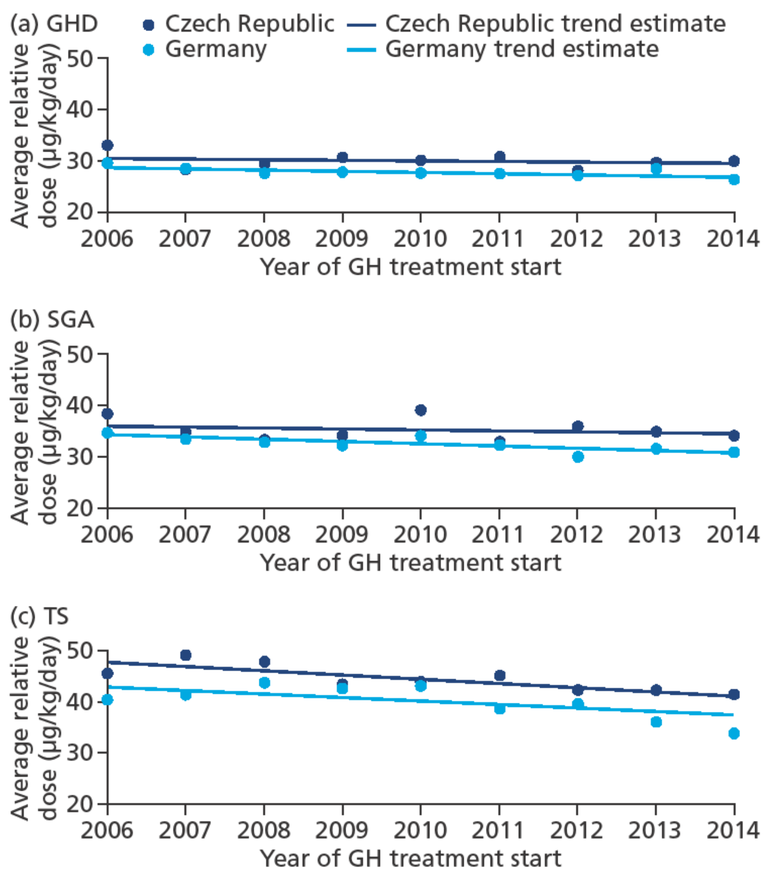
- This study included data for 2113 patients from Germany (GHD, n=1321 [69.6% male]; SGA, n=657 [59.1% male]; TS, n=135) and 581 patients from the Czech Republic (GHD, n=308 [68.5% male]; SGA, n=214 [52.8% male]; TS, n=59).
- Age at treatment start: in Germany a significant reduction from 2006 to 2014 in mean [SD] age (years) at treatment start was observed for children with GHD (10.0 [3.9]: 8.3 [4.1]; $p<0.001$) and children born SGA (7.5 [3.2]: 6.6 [2.4]; $p=0.025$). In the Czech Republic a significant decrease over time was observed for children with GHD (11.4 [3.6]: 6.9 [4.1]; $p<0.001$) only. There was no significant change in age at treatment start over time observed in either country for patients with TS (Figure 1).
- Baseline GH dose: in Germany significant reductions from 2006 to 2014 in mean [SD] baseline GH dose (µg/kg/day) in patients with GHD (29.4 [7.4]: 26.3 [3.7]; $p=0.029$) and SGA (34.7 [4.4]: 30.9 [4.4]; $p=0.012$) were observed. In the Czech Republic a significant reduction in mean baseline GH dose over time was observed in patients with TS (45.6 [3.7]: 41.6 [3.5]; $p=0.005$) only (Figure 2). It is unclear whether this reduction of <10% is clinically significant.
  - Comparison of trends in mean baseline GH dose between Germany and the Czech Republic over time showed significant between-country differences for GHD ($p<0.001$), SGA ($p<0.001$) and TS ($p=0.006$). In general, mean GH doses at baseline were higher in the Czech Republic than in Germany for all indications.
- Height SDS at treatment start: comparison of trends in height SDS at treatment start over time between Germany and the Czech Republic revealed significant between-country differences for children with GHD ($p=0.013$). Height SDS at treatment start in GHD was higher in Germany than in the Czech Republic in 2006, but was significantly reduced over time in Germany ($p=0.028$) and approached the same level as height SDS at treatment start in the Czech Republic by 2014 (Figure 3).
  - No time trend or between-country difference in height SDS at treatment start was observed in patients born SGA (Figure 3).
  - In patients with TS, height SDS at treatment start was generally lower in Germany than in the Czech Republic and a significant between-country difference in height SDS at treatment start was observed ($p=0.018$) (Figure 3).

Figure 1 Linear regression plots showing estimated mean age at treatment start (2006–2014) for patients in Germany and the Czech Republic: (a) GHD; (b) SGA; (c) TS.



GHD, growth hormone deficiency; SGA, small for gestational age; TS, Ullrich–Turner syndrome.

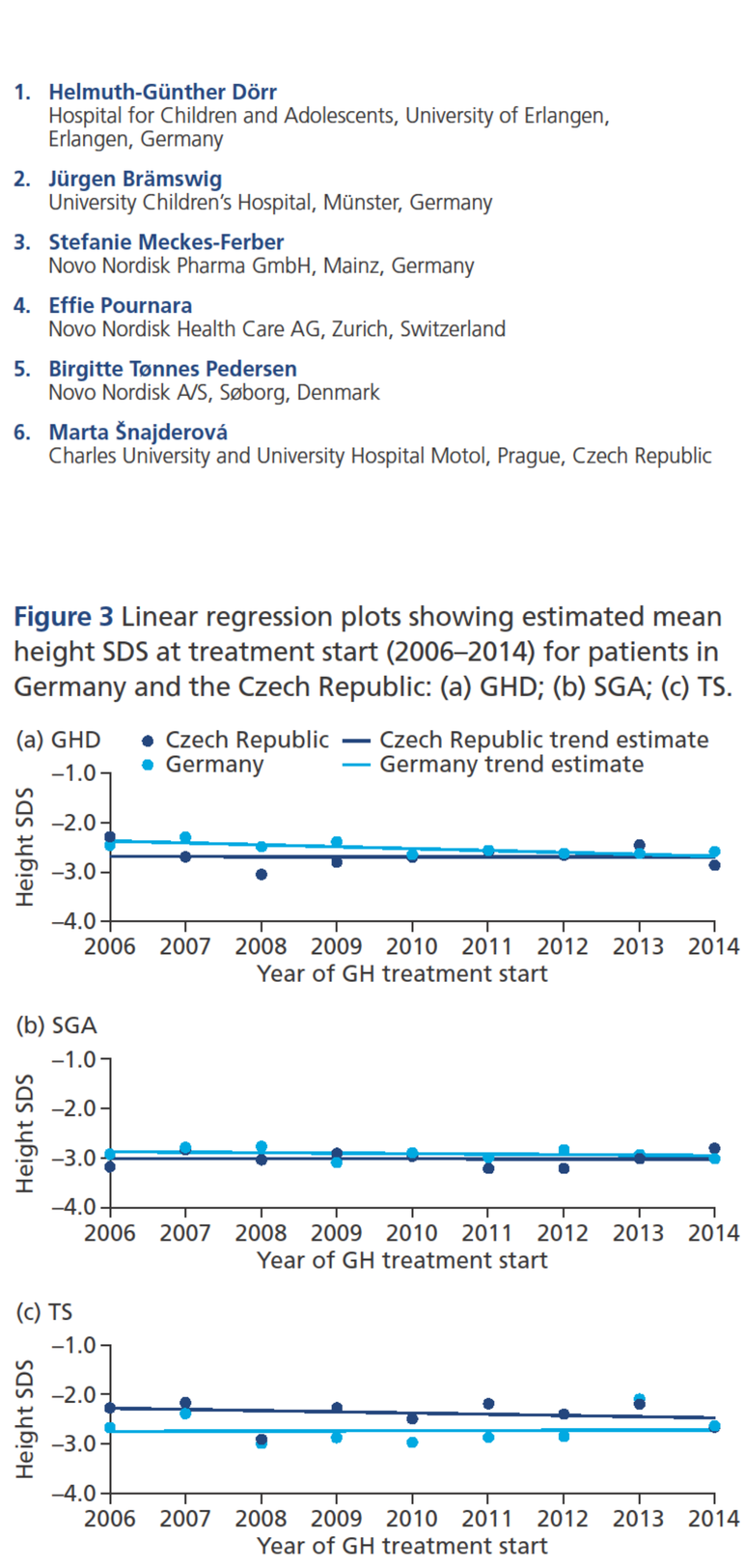
Figure 2 Linear regression plots showing estimated mean GH dose at treatment start (2006–2014) for patients in Germany and the Czech Republic: (a) GHD; (b) SGA; (c) TS.



GHD, growth hormone deficiency; SGA, small for gestational age; TS, Ullrich–Turner syndrome.

- Increasing proportions of females with GHD (2006: 2014) (16.7%: 32.4%) and born SGA (21.4%: 66.7%) were enrolled in the Czech Republic during the study, bringing proportions closer to those observed in Germany for children with GHD (27.8%: 29.6%) and born SGA (37.7%: 40.9%).
- BMI SDS at treatment start did not change significantly over time or differ significantly between countries (Germany mean [SD]; Czech Republic mean [SD]) for patients with GHD (–0.16 [1.27]; –0.12 [1.36]), born SGA (–0.87 [1.29]; –0.94 [1.23]) or with TS (0.31 [1.19]; 0.41 [1.20]) between 2006 and 2014.

Figure 3 Linear regression plots showing estimated mean height SDS at treatment start (2006–2014) for patients in Germany and the Czech Republic: (a) GHD; (b) SGA; (c) TS.



GHD, growth hormone deficiency; SDS, standard deviation scores; SGA, small for gestational age; TS, Ullrich–Turner syndrome.

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Conclusions

- Although the data described here suggest an improvement in the age of diagnosis and treatment start for patients with GHD and SGA there remains a need for increased awareness of the importance of early diagnosis and treatment start for patients with TS.
- The reason for the decrease over time of the baseline GH dose in girls with TS in the Czech Republic and in children with GHD or born SGA in Germany, is unclear and thus warrants further investigation.
- The improvement in the proportion of girls receiving GH therapy in the Czech Republic, such that it is comparable with that in Germany, may be a further example of raised awareness in the treatment of growth disorders in the Czech Republic over the last decade.

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