Status of the growth hormone/ insulin-like growth factor-1 (GH/IGF-1) axis in relation to growth failure, body weight and neuroprotection in children with Ataxia telangiectasia

Short title: Growth hormone in AT (GHAT)

Author: Stefan Zielen and Ralf Schubert

Development phase: IV

EudraCT number: 2009-015739-34

Studycode: FRA.GHAT.2009

Study Type: Interventional

Study Design: Open diagnostic treatment, Safety/Efficacy Study

Official Title: **Status of the growth hormone/ insulin-like growth factor-1 (GH/IGF-1) axis in relation to growth failure, body weight and neuroprotection in children with Ataxia telangiectasia**

Primary Outcome Measures:

- The primary objective is to evaluate the GH increase after Arginine Provocation Test

Secondary Outcome Measures:

- The secondary objective is the GH increase after Clonidine Provocation Test
- To evaluate the safety and efficacy of the IgF-1 generation test.
- To correlate GH/IGF-1 deficiency to BMI
- To correlate GH/IGF-1 deficiency to MRI findings

Explorative Measures:

- Restoration of immune function (increase of CD4 and CD8 cells) during IGF-1-generation test.

Intervention Details:

Drug: Growth Hormone (GH)

Procedure: Arginine Provocation Test

Procedure: Clonidine Provocation Test

Procedure: IGF-1 Generation Test

Detailed Description:

Growth failure and GH/IgF-1 deficiency has been described in patients diagnosed with Ataxia telangiectasia (AT) (1). This study will evaluate the status of the **growth hormone/ insulin-like growth factor-1 (GH/IGF-1**) axis in relation to growth failure, body weight and composition and neuroprotection in children with Ataxia telangiectasia (AT).

Patients ages 3 to 18 who have not yet begun puberty, have a diagnosis of AT, and may show reduced growth velocity (measured as linear growth that is less than 10% of that expected for children of the same age group, over the past 12 months) may be eligible for this study. This diagnostic study will performed as outlined. Patients will have a physical history and exam, blood tests, and body measurements and MRI of the brain if indicated..

Patients (girls < 8 and boys < 10 years) will take estradiol orally for 2 days, to help avoid false results of growth hormone (GH) levels in blood samples. Then provocation testing is done, with two tests back to back. It determines blood levels of GH and the body's response to testing with drugs called arginine and clonidine. Patients are admitted to the pediatric inpatient unit and will have an intravenous (IV) line placed in the arm. Arginine is given by IV over 30 minutes, and blood samples are taken. Right after arginine testing, the clonidine tablet is given. The **IGF-1** generation test is then done to see if the body makes **IGF-1** as a product in response to injections of GH for 5 consecutive days. This test does not require that patients are inpatients.

Eligibility

Ages Eligible for Study:	3 Years to 18 Years
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria

- INCLUSION CRITERIA:

Participants Must:

- Have a diagnosis of AT
- Have no fusion of epiphyses/closed growth plates as determined by X-ray of left wrist and hand (special skeletal age film)
- Be between 3 years to 18 years old and have not completed puberty
- Consent to permit blood and/or tissue samples for storage
- Demonstrate growth failure: height below the 10th percentile for chronological age
- Demonstrate growth failure, defined as growth velocity (measured as linear growth) that is less than 5% to 10% of that expected for children of the same age group, over the past 12 months

- Willingness to remain hospitalized for several days
- Provide evidence of serum IGF-1 level performed within the preceding 6 months and the results fall below 25% range of normal limits for age

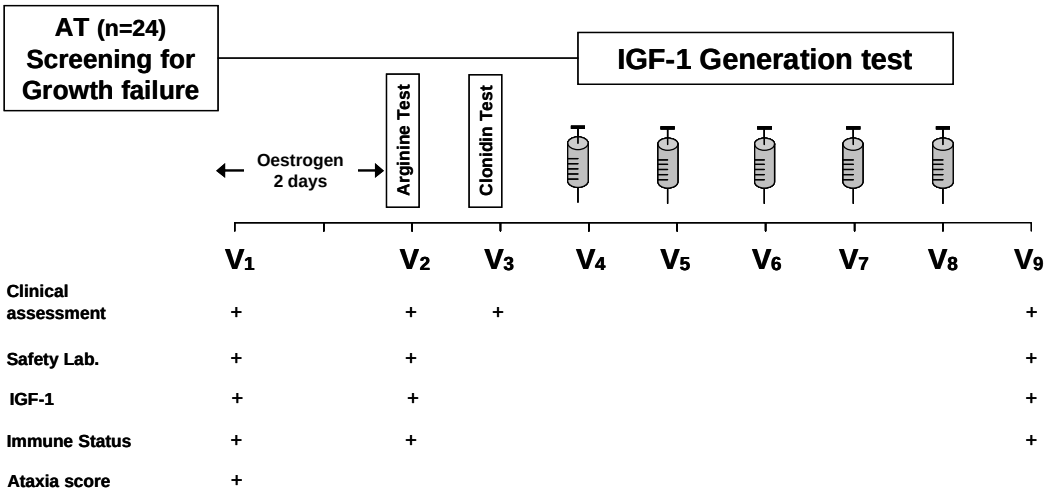
EXCLUSION CRITERIA:

Participants Must NOT:

- Have fusion of epiphyseal plates
- Be under the age of 3 years or have reached completion of puberty
- Have a serum IGF-1 level that is above the 25% range of normal limits for age
- Be above the 10th percentile height for chronological age
- Demonstrate any history of anaphylactic reaction or hypersensitivity to one of the GH formulation
- Have any active or suspected neoplasia
- Have any condition that, in the investigator's opinion, places the patient at undue risk by participating in the study
- Be unwilling to undergo testing or procedures associated with this protocol
- Have acute or chronic infections
- Have a hypersensitivity to one of the drugs: Clonidinhydrochlorid, Argininhydrochlorid, Estradiolvalerat, Somatropin
- Have a presence of bradycardia, cardiac arrhythmia, have symptoms of a sick sinus syndrome
- Have acute liver diseases

Study design:

IGF-1: growth failure, body weight and composition and neuroprotection in children with Ataxia telangiectasia (AT)



MRT during V1-V9 only if clinical indicated and not done in the last 12 months

Fig. 1

References

[1] Boder, E. and Sedgwick, R.P. (1958) Ataxia-telangiectasia; a familial syndrome of progressive cerebellar ataxia, oculocutaneous telangiectasia and frequent pulmonary infection. Pediatrics. 21, 526–554.
[2] Lavin, M.F. (2008) Ataxia-telangiectasia: from a rare disorder to a paradigm for cell signalling and cancer. Nat. Rev. Mol. Cell Biol. 9, 759–769.
[3] Schubert, R., Reichenbach, J., Zielen, S. (2005) Growth factor deficiency in patients with ataxia telangiectasia. Clin. Exp. Immunol. 140, 517–519.
[4] Isgaard, J., Aberg, D., Nilsson, M. (2007) Protective and regenerative effects of the GH/IGF-I axis on the brain. Minerva Endocrinol. 32, 103–113.
[5] Yang, D.Q. and Kastan, M.B. (2000) Participation of ATM in insulin signalling through phosphorylation of eIF-4E-binding protein 1. Nat. Cell Biol. 2, 893–898.
[6] Peretz, S., Jensen, R., Baserga, R., Glazer, P.M. (2001) ATM-dependent expression of the insulin-like growth factor-I receptor in a pathway regulating radiation response. Proc. Natl. Acad. Sci. U.S.A. 98, 1676–1681.
[7] Shahrabani-Gargir, L., Pandita, T.K., Werner, H. (2004) Ataxia-telangiectasia mutated gene controls insulin-like growth factor I receptor gene expression in a deoxyribonucleic acid damage response pathway via mechanisms involving zinc-finger transcription factors Sp1 and WT1. Endocrinology 145, 5679–5687.
[8] Suzuki, A., Kusakai, G., Kishimoto, A., Shimojo, Y., Ogura, T., Lavin, M.F., Esumi, H. (2004) IGF-1 phosphorylates AMPK-alpha subunit in ATM-dependent and LKB1-independent manner. Biochem. Biophys. Res. Commun. 324, 986–992.
[9] Kieslich M, Hoche F, Reichenbach J, Weidauer S, Porto L, Vlaho S, Schubert R, Zielen S. (2009) Extracerebellar MRI-lesions in ataxia telangiectasia go along with deficiency of the GH/IGF-1 axis, markedly reduced body weight, high ataxia scores and advanced age**.** Cerebellum. Nov 7. [Epub ahead of print]
[10] Schubert R, Schmitz N, Pietzner J, Tandi C, Theisen A, Dresel R, Christmann M, Zielen S. (2009) Growth hormone supplementation increased latency to tumourigenesis in Atm-deficient mice. Growth Factors. 2009 ;27(5):265-73.

Contacts and Locations

Prof. Dr. Stefan Zielen and Dr. Ralf Schubert
Zentrum für Kinder- und Jugendmedizin
Allergologie, Pneumologie und Mukoviszidose
Klinikum der Johann Wolfgang Goethe-Universität
Theodor-Stern-Kai 7,
60590 Frankfurt/Main
Tel.: 069/6301-83063,
Fax: 069/6301-83349
Stefan.Zielen@kgu.de