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RESEARCH REPORT

Beneficial Effect of BH_4 Treatment in a 15-Year-Old Boy with Biallelic Mutations in *DNAJC12*

Monique G. M. de Sain-van der Velden · Willemijn F. E. Kuper · Marie-Anne Kuijper · Lenneke A. T. van Kats · Hubertus C. M. T. Prinsen · Astrid C. J. Balemans · Gepke Visser · Koen L. I. van Gassen · Peter M. van Hasselt

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Abstract *Background*: Biallelic mutations in *DNAJC12* were recently identified as a BH_4-responsive cause of hyperphenylalaninemia (HPA). Outcome was only favorable when treatment was initiated early in life. We report on a 15-year-old boy with HPA due to a homozygous deletion in *DNAJC12* in whom – despite his advanced age – treatment was initiated.
Case: A boy with developmental delay, an extrapyramidal movement disorder, and persistently elevated plasma phenylalanine levels was diagnosed with *DNAJC12* deficiency at the age of 15 years. Diagnosis was made upon exome reanalysis revealing a homozygous 6.9 kb deletion in *DNAJC12* which had not been detected by the standard exome analysis pipeline. Treatment with the BH_4 analog sapropterin dihydrochloride (10 mg/kg/day) was initiated and evoked a 50% reduction of the plasma phenylalanine levels. More strikingly, a marked improvement in daily functioning and improved exercise tolerance was noted. Additionally, gait analysis before and after treatment initiation revealed a partial normalization of his movement disorder.
Conclusion: Patients with hyperphenylalaninemia due to *DNAJC12* deficiency may benefit from treatment with a BH_4 analog – even when introduced at a later age.

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"Monique G. M. de Sain-van der Velden" and "Willemijn F. E. Kuper" contributed equally to this work.

M. G. M. de Sain-van der Velden · H. C. M. T. Prinsen · K. L. I. van Gassen
Department of Genetics, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands
e-mail: M.G.deSain@umcutrecht.nl; B.Prinsen@umcutrecht.nl; K.L.I.vanGassen-2@umcutrecht.nl

W. F. E. Kuper · G. Visser · P. M. van Hasselt (✉)
Department of Metabolic Diseases, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands
e-mail: w.f.e.kuper@umcutrecht.nl; G.Visser-4@umcutrecht.nl; p.vanhasselt@umcutrecht.nl

M.-A. Kuijper · L. A. T. van Kats · A. C. J. Balemans
Centre of Excellence for Rehabilitation Medicine Utrecht, Rehabilitation Centre De Hoogstraat, Utrecht, The Netherlands
e-mail: m.a.kuijper@dehoogstraat.nl; l.v.kats@dehoogstraat.nl; a.balemans@vumc.nl

A. C. J. Balemans
Department of Rehabilitation Medicine, Amsterdam Movement Sciences, VU University Medical Center, Amsterdam, The Netherlands

Introduction

Recently, biallelic mutations in *DNAJC12* (OMIM #606060) were identified as a cause of (moderate) hyperphenylalaninemia (HPA) clinically and biochemically mimicking the tetrahydrobiopterin (BH_4) metabolism disorders putatively due to an interacting function of *DNAJC12* with phenylalanine hydroxylase (PAH), tyrosine hydroxylase and tryptophan hydroxylase (Anikster et al. 2017; Blau 2016; Longo 2009; Kaufman et al. 1978; Ng et al. 2015). The currently described phenotypic spectrum of *DNAJC12* deficiency ranges from intellectual disability and severe neurological symptoms (Anikster et al. 2017) to a very mild neurological phenotype (van Spronsen et al. 2017) or early onset parkinsonism (Straniero et al. 2017). A favorable outcome could be achieved when treatment including a BH_4 analog was initiated early in life (Anikster et al. 2017). Here, we describe in a patient with HPA due to biallelic mutations in *DNAJC12* the beneficial effects of treatment with a BH_4 analog even when initiated later in life.

Case

The patient, a boy born to consanguineous Moroccan parents, was referred to our department because of development delay and a movement disorder at the age of 7 years. Development during the first years of his life was reportedly normal. Clinical features at presentation included an extrapyramidal movement disorder with continuous involuntary movements and dysarthria. In addition, he was reported to be socially withdrawn. Although newborn screening for phenylketonuria (PKU) had been negative, metabolic investigations performed at 7 years of age revealed an increased phenylalanine concentration in plasma (564 μmol/L, normal <98 μmol/L), urine (69 mmol/mol creatinine, normal <20 mmol/mol creatinine), and cerebrospinal fluid (CSF) (92 μmol/L, normal <16 μmol/L). Additional investigations in CSF showed a decreased 5-hydroxyindoleacetic acid concentration (13 nmol/L, normal: 50–300 nmol/L) with normal concentrations of homovanillic acid (119 nmol/L, normal: 100–800 nmol/L), neopterin (15 nmol/L, normal: 9–20 nmol/L), and biopterin (26 nmol/L, normal: 10–34 nmol/L). To unravel a BH_4 metabolism defect a combined phenylalanine-BH_4 loading test was performed. Three hours after oral phenylalanine loading (100 mg/kg body weight), synthetic BH_4 was administered orally (at a dose of 20 mg/kg body weight). Phenylalanine concentration decreased by 22 and 55%, 4 and 8 h after BH_4 administration, respectively. A similar pattern has been described in patients with dihydropteridine reductase (DHPR) deficiency but DHPR activity was normal and no mutations were found in the *QDPR* gene, nor in the other known genes associated with HPA (i.e., *PAH*, *GCH1*, *PTS* and *PCB1*) (Ponzone et al. 1993). Additional genetic investigations over the years, including SNP array analysis and diagnostic whole exome sequencing, did not lead to a diagnosis. Based on the recent identification of biallelic mutations in *DNAJC12* as a cause of a BH_4-like neurological disorder including moderate HPA, we reanalyzed the exome variant data of this patient and found no mutations. Visual inspection of the bam alignment file, however, showed a homozygous deletion of approximately 7 kb. This appeared to be the same deletion as the deletion described, also in patients of Moroccan descent (Anikster et al. 2017). Indeed, PCR and Sanger sequencing validation showed that it was identical. The nomenclature according to the human genome variation society (www.hgvs.org) is, however, NM_021800.2: c.298-953_503-2589del p.(?). The deletion is flanked by a homologous sequence, suggesting that the deletion occurred by homologous recombination. Such deletions will not be detected by standard exome variant calling pipelines.

This diagnosis prompted initiation of treatment with sapropterin dihydrochloride (KUVAN®), a synthetic BH_4 analog, at a dose of 10 mg/kg/day in the patient, now aged 15 years. Phenylalanine concentrations, which had been stable (556 ± 51 μmol/L) for years, dropped to 209–315 μmol/L within 2 weeks. More importantly, a clear clinical improvement was noticed. Before treatment, the patient was introverted and had exhibited debilitating fatigue, requiring afternoon naps. Strikingly, exercise provoked a severe exhaustion resulting in a decreased consciousness which was confirmed when performing an exercise test. Within days after initiation of treatment with the BH_4 analog, he became more energetic, no longer needing his afternoon naps, showing more initiative. In addition, contact with others clearly improved. Exercise testing conducted 4 weeks after treatment initiation confirmed an increased power (+33%) and an increased aerobic capacity (+15%) (Brehm et al. 2014; McGinley et al. 2009). In addition, there was a measurable improvement of the movement disorder, as underlined by gait analysis, showing a disappearance of a (pathological) early heel-rise in midstance and an improvement of knee flexion in loading response (see Fig. 1). The positive effects were still present at latest follow-up 8 months after treatment initiation including stable and slightly improved outcomes on gait and exercise analysis.

Discussion

We report on the beneficial effects of treatment with a BH_4 analog initiated later in life in a patient with HPA due to biallelic mutations in *DNAJC12*. Patient and parent reported improvements were quantified using gait and exercise analysis demonstrating both an improvement of the patients' movement disorder and an overall increase in strength and fitness.

Although, obviously, treatment initiated at this age cannot undo irreversible damage due to *DNAJC12*-associated metabolic processes, the effects in our patient suggest it can ameliorate the acute effects of a deficiency and may be able to prevent further damage. This observation nuances the statement by Anikster et al. that late treatment cannot resolve the resulted developmental delay (Anikster et al. 2017).

In contrast to previous patients, who received a mixture of treatments precluding conclusions regarding the added value of each of these treatments, our patient's treatment consisted solely of BH_4 supplementation. This suggests that BH_4 – rather than neurotransmitter supplementation – plays a central role in treatment outcome, possibly by making BH_4 associated reactions more favorable allowing more substrate to be converted into product. In addition, the positive short-term effect observed in our patient suggests that this treatment could also influence symptoms in milder forms of *DNAJC12*-associated HPA (van Spronsen et al. 2017; Straniero et al. 2017). Identification of additional

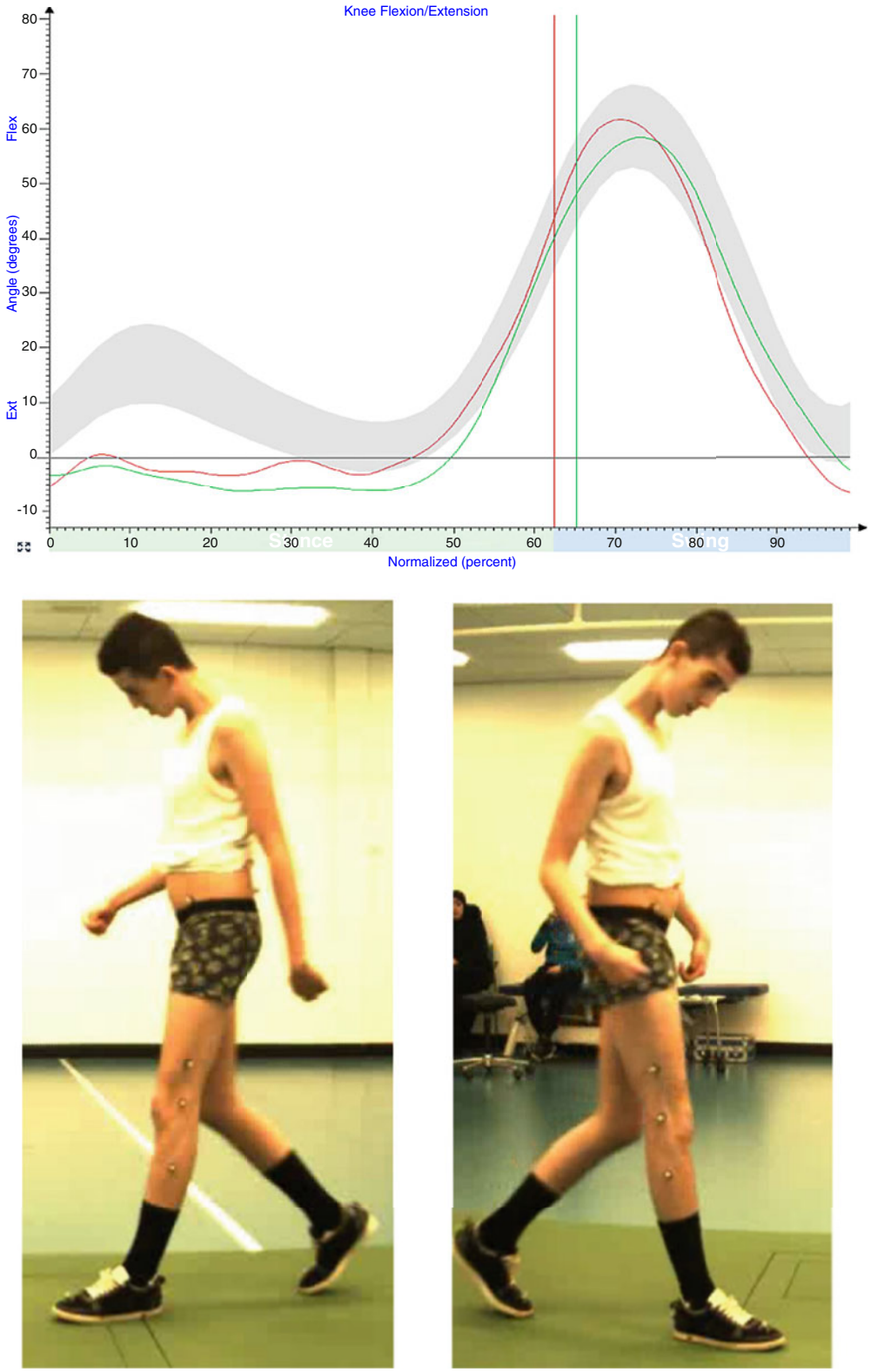

Fig. 1 Improved knee flexion in stance after treatment in a patient with hyperphenylalaninemia due to biallelic mutations in *DNAJC12*. Knee angle in the sagittal plane during gait prior to treatment (left) and 4 weeks after treatment initiation (right) demonstrating less hyperextension of the knee. Upper panels represent three-dimensional gait analysis. Red = left leg. Green = right leg. Gray = reference values. Representative photographs are provided in the lower panels. Instrumented gait analysis was performed with an 8-camera system (Vicon Motion Systems, Lake Forest, CA), all kinematic data was processed using Vicon Plug-in-gait Lowerbody Model

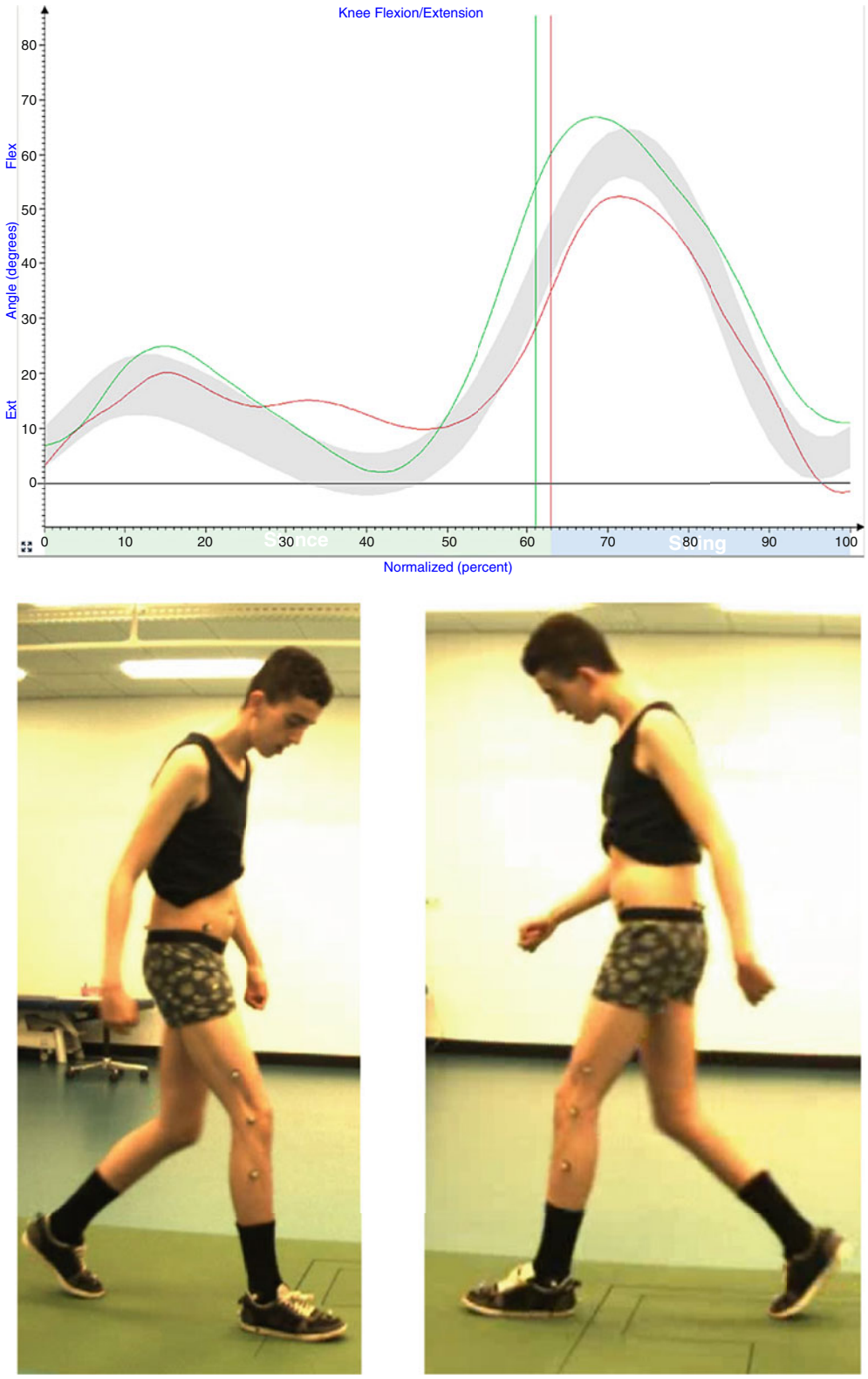

Fig. 1 (continued)

cases of HPA due to biallelic mutations in *DNAJC12* will be needed to elucidate the remaining therapeutic window in late identified cases.

It is noteworthy that our patient was not identified by population newborn screening, which was also reported in one of the six patients described by Anikster et al. (2017). Analysis for *DNAJC12* variants should be included in the differential diagnosis of HPA. The 6.9 kb microdeletion found in our case was initially also missed as the previously reported cases sharing this mutation (Anikster et al. 2017). Therefore, diagnostics for the *DNAJC12* gene should include a test that can detect this deletion, in particular in a patient of Moroccan descent. Current exome variant calling pipelines usually fail to recognize small microdeletions.

In summary, our report highlights the beneficial effect of treatment with a BH_4 analog in a patient with biallelic mutations in *DNAJC12* – even though treatment was only introduced later in life.

Synopsis

Treatment with a BH_4-analog only in a patient with *DNAJC12* deficiency diagnosed in puberty has a beneficial effect.

Compliance with Ethics Guidelines

Conflict of Interest

Monique G. M. de Sain-van der Velden, Willemijn F. E. Kuper, Marie-Anne Kuijper, Lenneke A. T. van Kats, Hubertus C. M. T. Prinsen, Astrid C. J. Balemans, Gepke Visser, Koen L. I. van Gassen, and Peter M. van Hasselt declare that they have no conflict of interest.

Informed Consent

Parents provided informed consent prior to article submission to use their child's history information, metabolic and genetic test results and photographs. Signed consent form for publication was obtained.

This article does not contain any studies with human or animal subjects performed by any of the authors.

Details of the Contributions of Individual Authors

Monique de Sain-van der Velden performed the metabolic investigations and drafted and revised the manuscript.

Willemijn Kuper supported Peter van Hasselt in the clinical care for the patient and drafted and revised the manuscript.

Marie-Anne Kuijper is the rehabilitation physician who provided clinical care for the patient in the rehabilitation center, contributed to the figure and revised the manuscript.

Koen van Gassen performed the genetic investigation that demonstrated the homozygous deletions in *DNAJC12* and revised the manuscript.

Lenneke van Kats performed the movement analyses contributing to the figure and revised the manuscript.

Astrid Balemans performed the movement analyses contributing to the figure and revised the manuscript.

Gepke Visser supported Peter van Hasselt in the clinical care for the patient and revised the manuscript.

Berthil Prinsen contributed in the metabolic investigations and revised the manuscript.

Peter van Hasselt is the pediatrician metabolic diseases who provided clinical care for the patient and revised the manuscript.

Corresponding Author

Peter M. van Hasselt.

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