厚生労働科学研究費補助金（難治性疾患等政策研究事業）
分担研究報告書

プラダー・ウィリ症候群における診療ガイドラインの作成に関する研究：体組成分野

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研究要旨
プラダー・ウィリ症候群（Prader-Willi Syndrome: PWS）は、15 番染色体短腕 q11-q13 に位置する父由来で発現する複数の遺伝子の作用が消失することにより発症する疾患で、15q11-q13 の父性染色体微細欠失、15 番染色体の母性片側性ダイソミーや刷り込み異常などが原因となる。新生児期に筋緊張低下で発見されることが多く、特異的顔貌、精神運動発達遅滞、哺乳力低下などの臨床症状や遺伝学的検査で診断される。幼児期より過食に伴う肥満が出現し、糖尿病、高脂血症の合併率が高く、生涯にわたる栄養・体重管理が必要である。それ以外にも、低身長、性腺機能低下などの内分泌学的異常をきたす。
PWS では、肥満が出現する以前の乳児期から、体組成の悪化、つまり脂肪量の増加を認め、過食とともに肥満となり、更なる体組成の悪化をきたす。体組成の悪化、肥満の進行に伴い糖尿病、高血圧、高脂血症などの合併症が多くなることが報告されており、体組成・肥満の管理は PWS 患者の QOL を規定する大きな因子である。本分担研究では PWS 診療の標準化をめざし、PWS 診療ガイドラインの体組成分野を担当し、作成する。これまでに、クリニカルクエスチョン（CQ）を設定し、論文の抽出、システマティックレビューを行った。今後、推奨レベルの検討、ガイドラインの文書化を行う予定である。

Ａ．研究目的
プラダー・ウィリ症候群（Prader-Willi Syndrome: PWS）における診療ガイドラインの作成：体組成分野

Ｂ．研究方法
PWSの診療ガイドラインにおける体組成分野に関わるクリニカルクエスチョン（CQ）を設定した。CQに関わる論文を抽出し、システマティックレビューを行い、推奨レベルの検討を実施する。

Ｃ．研究結果
1.　体組成分野のCQとして以下の9つを策定した。
CQ1 体組成改善は食事・運動療法で可能であるか？
CQ2　GH治療は体組成改善に貢献するか？
CQ3　GH治療の早期開始は体組成改善に有効か？
CQ4　GH治療は身長に拘らず行うべきか？
CQ5　GH治療は成人年齢でも行うべきか？
CQ6　体組成が改善することのメリットは？
CQ7　GH治療で体組成が改善した。終了後は元に戻ってしまうか？
CQ8　GH治療終了後、基礎代謝が下がり続け、徐々に体重が増えている。原因は？（食事量は従前通りとして）
CQ9　成人にも低量投与して体組成を改善することこそPWS児を育てる親の希望につながるのではないか？
2.　上記のCQに対する論文の抽出を行った。
CQ1: 体組成改善は食事・運動療法で可能であるか？
CQ1-1食事療法
検索式：
Prader-Willi syndrome AND Nutritional management
OR
Prader-Willi syndrome AND Nutritional intervention
103本の論文のうち12本を抽出
1. Irizarry KA et al. Prader Willi Syndrome: Genetics, Metabolomics, Hormonal Function, and New Approaches to Therapy. Adv Pediatr. 2016 Aug;63(1):47-77.
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CQ1-2 運動療法

検索式： Prader-Willi syndrome AND Exercise

７５本の論文中、21本を抽出+1本追加し、計２２本

1. Hyde AM et al. Metabolic responses to walking in children with Prader-Willi syndrome on growth hormone replacement therapy. Am J Med Genet A. 2018 Oct 22:e40509.
2. Woods SG et al. The associations between diet and physical activity with body composition and walking a timed distance in adults with Prader-Willi syndrome. Food Nutr Res. 2018 Jun 18;62.
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4. Hyde AM et al. Ventilatory Responses During Submaximal Exercise in Children With Prader-Willi Syndrome.Pediatr Exerc Sci. 2018 Aug 1;30(3):411-417.
5. Rubin DA et al. Hormonal and Metabolic Responses to a Single Bout of Resistance Exercise in Prader-Willi Syndrome. Horm Res Paediatr. 2017;87(3):153-161.
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7. Duran AT et al. Association between physical activity and bone in children with Prader-Willi syndrome. J Pediatr Endocrinol Metab. 2016 Jul 1;29(7):819-26.
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21. Yamagishi M et al. A new diet-exercise therapy in our obese-child clinic. J UOEH. 1987 Jun 1;9(2):215-25.
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CQ2:　GH 治療は体組成改善に貢献するか？
CQ4:　GH治療は身長に拘らず行うべきか？
CQ6：体組成が改善することのメリットは？
上記3つは同じ検索式を用いた
検索式：
Prader-Willi syndrome AND growth hormone
OR
Prader-Willi syndrome AND GH
Limitation: Clinical Trial AND Age: birth to 18 years
64文献中、26文献を抽出

1. Bakker NE et al. Beneficial Effect of Growth Hormone Treatment on Health-Related Quality of Life in Children with Prader-Willi Syndrome: A Randomized Controlled Trial and Longitudinal Study. Horm Res Paediatr. 2015;84(4):231-9.
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4. Reus L et al. Growth hormone therapy, muscle thickness, and motor development in Prader-Willi syndrome: an RCT. Pediatrics. 2014 Dec;134(6):e1619-27.
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17. Höybye C. Endocrine and metabolic aspects of adult Prader-Willi syndrome with special emphasis on the effect of growth hormone treatment.Growth Horm IGF Res. 2004 Feb;14(1):1-15.
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Dis Child. 1998 May;78(5):474-6.
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26. Lindgren AC et al. Effects of growth hormone treatment on growth and body composition in Prader-Willi syndrome: a preliminary report. The Swedish National Growth Hormone Advisory Group. Acta Paediatr Suppl. 1997 Nov;423:60-2.

CQ3:　GH 治療の早期開始は体組成改善に有効か？

検索式：

Prader-Willi syndrome AND growth hormone

OR

Prader-Willi syndrome AND GH

Limitation: Clinical Trial AND Age: birth-23 months

18文献中、8文献を抽出

1. Reus L et al. Growth hormone therapy, muscle thickness, and motor development in Prader-Willi syndrome: an RCT. Pediatrics. 2014 Dec;134(6):e1619-27.
2. Reus L et al. Growth hormone combined with child-specific motor training improves motor development in infants with Prader-Willi syndrome: a randomized controlled trial. Res Dev Disabil. 2013 Oct;34(10):3092-103.
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6. Carrel AL et al. Growth hormone improves mobility and body composition in infants and toddlers with Prader-Willi syndrome. J Pediatr. 2004 Dec;145(6):744-9.
7. Whitman B et al. Growth hormone improves body composition and motor development in infants with Prader-Willi syndrome after six months. J Pediatr Endocrinol Metab. 2004 Apr;17(4):591-600.
8. Eiholzer U et al. Growth hormone and body composition in children younger than 2 years with Prader-Willi syndrome. J Pediatr. 2004 Jun;144(6):753-8.

以下、成人 PWS における GH 治療の CQs

CQ5: GH治療は成人年齢でも行うべきか？

CQ7: GH治療で体組成が改善した。終了後は元に戻ってしまうか？

CQ8:GH治療終了後、基礎代謝が下がり続け、徐々に体重が増えている。原因は？（食事量は従前通りとして）

CQ9:成人にも低量投与して体組成を改善することこそPWS児を育てる親の希望につながるのではないか？

検索式：

Prader-Willi syndrome AND growth hormone

OR

Prader-Willi syndrome AND GH

Limitation: Clinical Trial AND Age: Adults 19+ years

18文献中、9文献を抽出

1. Kuppens RJ et al. Beneficial Effects of GH in Young Adults With Prader-Willi Syndrome: A 2-Year Crossover Trial. J Clin Endocrinol Metab. 2016 Nov;101(11):4110-4116.
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3. Olarescu NC et al. Dual-energy X-ray absorptiometry is a valid method to estimate visceral adipose tissue in adult patients with Prader-Willi syndrome during treatment with growth hormone. J Clin Endocrinol Metab. 2014 Sep;99(9):E1727-31.
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6. Sode-Carlsen R et al. One year of growth hormone treatment in adults with Prader-Willi syndrome improves body composition: results from a randomized, placebo-controlled study. J Clin Endocrinol Metab. 2010 Nov;95(11):4943-50.

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以下検索式：Prader-Willi syndrome AND Japanの中から、関連のあるものを抽出

10. Koizumi M, et al. Visceral adipose tissue increases shortly after the cessation of GH therapy in adults with Prader-Willi syndrome. Endocr J. 2018 Sep 4. doi: 10.1507/endocrj.EJ18-0107.
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Ｄ．考察

CQ 2, 5, 6に関しては十分なエビデンスレベルの高い論文が得られた。しかし、CQによってはエビデンスレベルの高い論文が必ずしも多くなかった（CQ1,3,4,7,8）。ほとんど論文を認めないCQも存在した（CQ9）。このようなCQに対しては、エキスパートオピニオンの形で対応が必要と考えられた。

Ｅ．結論

PWS の診療ガイドラインにおける体組成分野に関わる CQ の設定、論文抽出を行った。

Ｆ．研究発表

Koizumi M, Ida S, Shoji Y, Nishimoto Y, Etani Y,　Kawai M.　Visceral adipose tissue increases shortly after the cessation of GH therapy in adults with Prader-Willi syndrome.　Endocr J. 2018 29;65(11):1127-1137.

Ｇ．知的財産権の出願・登録状況（予定を含む。）

1. 特許取得
   無
2. 実用新案登録
   無
3. その他