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ORIGINAL ARTICLE

ADHD, learning difficulties and sleep disturbances associated with *KCNJ11*-related neonatal diabetes

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Objectives: Mutations in *KCNJ11* are the most common cause of permanent neonatal diabetes mellitus (NDM). Approximately 25% of patients have obvious neurological dysfunction, but whether milder related problems might be more common has been unclear. We sought to assess the prevalence of parental concerns about learning, behavior, attention deficit hyperactivity disorder (ADHD), social competency, and sleep in subjects with *KCNJ11*-related NDM compared to unaffected sibling controls.

Study design: Subjects or their guardians in the University of Chicago Monogenic Diabetes Registry completed a survey examining learning, behavior, ADHD and sleep. Thirty subjects with *KCNJ11*-related NDM and 25 unaffected sibling controls were assessed. Data were analyzed using GraphPad Prism 6. Nonparametric analysis was performed using Fisher's exact test for group comparisons.

Results: Thirteen (43%) individuals with *KCNJ11*-related NDM had treatment for or a diagnosis of ADHD compared to two (8%) of the sibling controls ($P < 0.05$). Compared to their sibling controls, individuals with *KCNJ11* mutations had significant differences in behavior difficulties, social awareness, academic achievement and the need for an Individualized Education Plan (IEP). As seen in other neurodevelopmental disorders, individuals with *KCNJ11* mutations also had significantly higher rates of sleep difficulties ($P < 0.01$).

Conclusion: Patients with *KCNJ11*-related NDM are at an increased risk for delays in learning, social-emotional and behavioral development, ADHD and sleep difficulties based on parent report. Early identification, along with integrated medical and developmental support, may promote better neurodevelopmental outcomes for this unique population. Further investigation utilizing detailed neuropsychological testing will better define the neurodevelopmental consequences of K_{ATP} mutations.

KEYWORDS

attention deficit disorder with hyperactivity, developmental disabilities, genetics, diabetes mellitus, permanent neonatal

INTRODUCTION

Neonatal diabetes mellitus (NDM), a genetic disorder characterized by the development of diabetes mellitus in the first 6 months of life, has been estimated in European populations to occur in 1 in 90 000–260 000 live births.[1,2] Mutations in the *KCNJ11* gene, encoding the Kir6.2 subunit of the ATP-sensitive potassium (K_{ATP}) channel, account for about 30% of cases of permanent NDM.[3,4] Most patients with *KCNJ11*-related NDM can be treated with oral sulfonylureas rather than insulin injections.[5]

K_{ATP} channels are found in the hippocampus, cerebral cortex, basal ganglia and cerebellum,[6,7] which is thought to explain the neurological dysfunction seen in some patients with *KCNJ11*-related NDM.[8] Approximately 25% of patients with a gene mutation of the K_{ATP} channel subunit have clearly identifiable neurological dysfunction: developmental delay, epilepsy and neonatal diabetes (DEND) is a

discrete syndrome describing the most severe clinical form of permanent NDM; intermediate DEND (iDEND) is a less severe phenotype without epilepsy.[9] Although the remaining 75% of cases have often been described as having diabetes in isolation, some reports have suggested that these cases may have milder impairment in the form of difficulties such as learning disorders and ADHD.[10] Indeed, in patients with K_{ATP} channel gene mutations who did not have DEND or iDEND, Busiah et al found some degree of neuropsychological dysfunction related to attention, learning, language and motor control.[11] Due to the rare nature of this condition, studies regarding the spectrum of developmental outcomes are limited and the aforementioned findings were reported in European populations. It remains unclear to what extent any mild neuropsychological dysfunction may result in actual functional impairment or if such patients fall within the spectrum of typical functioning. To further examine the consequences of possible underlying neuropsychological dysfunction in patients with NDM, we hypothesized that patients with *KCNJ11*-related mutations would be more likely to have attention, behavior, learning and social differences compared to healthy sibling controls. Although sleep disturbances have not been reported in this population, we also examined sleep because of the high prevalence of sleep disturbances in children with neurodevelopmental disabilities or diabetes.[12,13]

METHODS

Subjects with *KCNJ11*-related NDM and their unaffected siblings were consented for participation through the University of Chicago Monogenic Diabetes Registry (http://monogenicdiabetes.uchicago.edu/registry/). Participants in the registry were consented through protocols approved by the Institutional Review Board at the University of Chicago. The Registry uses surveys and medical records to collect longitudinal data about diagnosis, treatment, medical history, family history and genetic testing results.[14]

Using targeted parent/guardian questionnaires and a comprehensive health survey, subjects were assessed for learning and social abilities, behavior and attention problems, attention deficit hyperactivity disorder (ADHD) and sleep disturbances (Table S1 Supporting Information). Surveys were distributed via email and in person to subjects or their guardians. All subjects with *KCNJ11*-related NDM were receiving treatment with sulfonylurea medications.

The unique survey created for this study included the most relevant items from the Child Behavior Checklist (CBCL). The CBCL is a standardized form to assess behavior in children, as reported by parents and parent-surrogates. The reliability and validity of the CBCL has been demonstrated through a large body of research in both clinical and non-clinical populations.[15] Our survey utilized questions from the CBCL regarding social development and learning as well as additional questions assessing behavior, sleep, ADHD and medical and therapeutic services utilized by the subjects (Table S1).

Data were analyzed using GraphPad Prism 6 (GraphPad Software Inc, California http://www.graphpad.com). Nonparametric analysis was performed using Fisher's exact test for group comparisons, or the two-sample *t*-test when variables were normally distributed. Statistical significance was considered at $P < 0.05$.

RESULTS

Of the 459 individuals with an established monogenic etiology for diabetes within the University of Chicago Monogenic Diabetes Registry, 72 had a *KCNJ11* mutation. We distributed 121 surveys (72 subjects and 49 known sibling controls) and received 55 responses from 30 subjects, all with permanent neonatal diabetes (28 probands and 2 affected family members), and 25 unaffected sibling controls (Table 1). The non-responders consisted of 31 subjects with permanent neonatal diabetes (24 probands and 7 affected family members), 11 with transient neonatal diabetes (6 probands and 5 affected family members) and 24 unaffected control siblings. It is notable that all of the affected responders had a permanent neonatal diabetes phenotype, while none of those with transient diabetes responded. Among probands with permanent neonatal diabetes, there was a response rate of 54%, and responders ($n = 28$) and non-responders ($n = 24$) were similar by all characteristics, including household income and age at assessment (Table 1).

Compared to their sibling controls, individuals with *KCNJ11* mutations had significant differences in academic achievement and the need for an Individualized Education Plan (IEP), more behavior problems ($P < 0.001$), more symptoms and diagnoses of ADHD ($P < 0.001$) and higher rates of sleep difficulties ($P < 0.01$), per survey report (Table 2). When academic performance was considered compared to *peer* performance, individuals with *KCNJ11*-related NDM had significantly more difficulties in school than their siblings in several areas. Fourteen (60%) patients with NDM, compared to 2 (10%) of their sibling controls performed below their peers in reading ($P < 0.05$). Seventeen (74%) individuals with NDM and 2 (10%) sibling controls performed below their peers in math ($P < 0.001$). Handwriting was also more difficult for patients with NDM; 13 (56%) had skills below their peers compared to 4 (19%) of siblings ($P < 0.05$). English performance was below peer ability for 11 (47%) individuals with NDM and 2 (10%) of the sibling controls ($P < 0.01$). Finally, 10 (43%) individuals with NDM struggled with science compared to 1 (5%) of the sibling controls ($P < 0.01$).

Sixteen (53%) individuals with *KCNJ11*-related NDM had received occupational therapy, compared to 3 (14%) of their unaffected siblings ($P < 0.01$). Likewise, 14 (47%) patients with NDM required speech therapy, while only 3 (14%) of their unaffected siblings had received speech therapy. 35% of the patients with NDM did not have any friends as reported by their parents, and 30% had reported deficits in social awareness. The sibling controls did not lack friendships or appropriate social awareness.

Of the 30 patients with a *KCNJ11* mutation, 19 (63%) had behavior problems concerning to their parents. Only 4 (16%) of the unaffected siblings were reported to have behavior problems. Thirteen (43%) individuals with *KCNJ11*-related NDM had a diagnosis of ADHD or were being treated with medications and/or behavioral modifications for ADHD compared to 2 (8%) of the sibling controls, making ADHD significantly more prevalent in individuals with *KCNJ11* mutations ($P < 0.05$). Of the 11 patients with a diagnosis of ADHD, only 8 (77%) were receiving any type of treatment. Two patients with *KCNJ11* mutations did not have a clinical diagnosis of ADHD but were receiving pharmacological treatment for their ADHD symptoms.

TABLE 1 Characteristics of proband responders vs. non-responders and control responders[1]

	KCNJ11 PNDM survey responders (*N* = 28)	*KCNJ11* PNDM survey non-responders (*N* = 24)	Sibling control responders (*N* = 25)
Age at assessment (years)[2]			
Median	8.4	10.0	10.5
Interquartile range	5.9–12.5	5.4–18.8	7–15
Male sex—no. (%)[2]	12 (43)	15 (62)	12 (48)
Median household income (US$)[3]	70 519	67 243	
Standard deviation	56–108 000	51–92 000	
Age at NDM diagnosis (weeks)			
Median	7.8	9.9	
Interquartile range	4.7–15.1	5.6–16.6	
Age at sulfonylurea initiation (years)			
Median	1.2	2.5	
Interquartile range	0.3–5.6	0.6–13.7	
KCNJ11 mutation subtype			
R201H	9	5	
R201C	6	3	
V59M	6	5	
Other	7	11	

[1] All *P* values were >0.05 for all comparisons between PNDM proband responders vs non-responders.

[2] *P* values were >0.05 for proband responders vs control responders, and also for the total group of responder subjects (*n* = 30) vs control responders.

[3] Based on postal code; *P* > 0.05 (two-sample *t*-test).

TABLE 2 Neurodevelopmental findings

	KCNJ11 mutation (*N* = 30)	Sibling control (*N* = 25)	*P* value
ADHD diagnosis or treatment with ADHD medications and/or behavioral modifications (%)	13 (43)	2 (8)	<0.001
IEP evaluation (%)	20 (67)	2 (9)	<0.001
Sleep disturbance (%)	14 (47)	2 (9)	<0.01
Specialist care (%)			
Neurologist	11 (37)	0 (0)	<0.001
Developmental and behavioral pediatrician	11 (37)	2 (10)	<0.05
Psychologist	11 (37)	5 (24)	NS
Speech/language pathologist	14 (47)	3 (14)	<0.05
Occupational therapist	16 (53)	3 (14)	<0.01

ADHD, attention deficit hyperactivity disorder; IEP, individualized education program/plan; NS, not significant.

DISCUSSION

While childhood diabetes can be associated with cognitive dysfunction, it is mild in most cases and rarely meets criteria for clinically significant impairment.[16] Using a straightforward screening questionnaire, our study demonstrates that *KCNJ11*-related NDM may be associated with learning difficulties, disturbances in social-emotional and regulatory behaviors, an increase in ADHD symptoms and diagnosis and an increase in sleep difficulties. Although previous clinical and functional studies have suggested that certain more severely activating *KCNJ11* mutations are more likely to have obvious neurodevelopmental disability, we intentionally included all subjects within our Registry with any *KCNJ11* mutation. Children with the relatively common V59M mutation have uniformly been described as having developmental difficulties, whereas R201C cases are inconsistently reported as having challenges, and those with R201H mutations have usually been characterized as not having any clinically significant neurodevelopmental problems. The distribution of mutations in the current study reflected these more common mutations but the number of subjects was still too small to allow for reliable sub-group analysis; however, there was a wide distribution of reported difficulties amongst all mutation subtypes, including R201H. This supports our hypothesis that even the more mildly activating mutations may result in mild neurodevelopmental consequences. Studying larger groups of subjects of a variety of ages with more specific neuropsychological measures and comparison with siblings will further elucidate the consistency and breadth of impairment exhibited amongst those with K_{ATP} channel defects.

It is worth noting that none of the subjects with transient neonatal diabetes responded to the survey. Those with a transient diabetes phenotype typically have mutations that are less strongly activating in in vitro expression studies that tend to correspond to severity of

clinical phenotype. However, most reports have focused on the severe end of the spectrum and note that strongly activating mutations tend to have DEND-like neurological phenotypes,[17] whereas detailed information on neurodevelopment or neuropsychological testing for those with mild mutations is usually not reported. Given the natural history of the transient phenotype, it is likely that these subjects are not currently struggling with diabetes management but it is unknown whether they are also less likely to be facing neurodevelopmental struggles. It may therefore be possible that they were less motivated to respond to the survey addressing these concerns; however, the number of subjects with a transient history was low (six probands) and detailed testing of larger numbers of subjects are needed to determine the extent to which those with transient mild mutations exhibit any degree of neurodevelopmental impairment.

Academic difficulties associated with *KCNJ11*-related NDM occurred in the domains of reading, math, English and science. Compared to their unaffected siblings, more than 40% of the patients with NDM were below average in their academic achievement in these subjects, per parent report. Of these patients, 56% displayed poor handwriting skills, which may be a reflection of visual-motor deficits.[11] This is supported by the finding of poor hand–eye coordination associated with *KCNJ11*-related NDM.[18,19]

Parents reported behavior difficulties, lack of friendships and deficits in social awareness in their children with *KCNJ11*-related NDM far more often than in their unaffected children. Such challenges in social-emotional and regulatory behaviors have not been previously described with *KCNJ11*-related NDM, which underscores the importance of early neuropsychological assessment and continued monitoring in these patients.

In a previous study, attention deficits were found in 100% of those with *KCNJ11* mutations when given in-depth neuropsychological assessments.[11] Despite the high prevalence of symptoms and diagnosis of ADHD in our cohort of patients with NDM, only three quarters of these patients were receiving any kind of treatment for ADHD. This is concerning because untreated ADHD symptoms often lead to functional impairments in multiple domains. Self-esteem, social function and academic outcomes have all been shown to improve with treatment of ADHD.[20] As patients with *KCNJ11*-related NDM are already at risk for having functional impairments in learning, behaviors and socialization, proper vigilance is important to recognize and treat ADHD early. The discrepancy of identifying ADHD by in-depth assessment[11] vs parent report indicates the importance of neuropsychological monitoring in this at-risk population.

As has been seen in other studies of individuals with neurodevelopmental disabilities, sleep difficulties were more common among those children with a *KCNJ11* mutation in our study.[12] Although no other studies have looked at the impact of *KCNJ11*-related NDM on sleep, it may be that impairment of K_{ATP} channel function in the brain impacts sleep similarly to learning and behavior.

Neurodevelopmental concerns likely result from a direct effect of brain expression of mutated K_{ATP} channels in these patients, but other factors may contribute. Diabetic ketoacidosis, seizures and episodes of severe hypoglycemia early in life—a time of critical brain development—may also impact neuropsychological and developmental progress. Pearson et al found that most transitions from insulin to sulfonylureas are safe and highly effective in the short term for most patients with *KCNJ11* mutations.[3] In addition to potential neurodevelopmental improvements from sulfonylurea treatment, lifestyle changes could also significantly impact patients and their families. Management of NDM with sulfonylurea medications results in less frequent blood sugar monitoring and improved glycemic control, and a likely lower risk of short term and long-term complications. Furthermore, initiation of sulfonylurea therapy at a younger age allows for lower doses of medication and less need for additional medications.[21]

Modest improvements in cognitive and motor functioning occur in some affected patients after transition from insulin injection to oral sulfonylureas.[9,22] Slingerland et al found that transition from insulin to sulfonylureas positively impacted motor and cognitive function even in patients who were older than the time of critical brain development,[9] but the timing of medication transition may influence the degree of benefit possible and may also significantly influence social-emotional and regulatory behaviors. In this regard, our previous study suggested that visuomotor performance can be improved by early treatment (under one year of age) with sulfonylureas in patients with *KCNJ11*-related NDM.[18] Results of the current study demonstrated neurodevelopmental challenges in patients with KCNJ11 mutation subtypes not previously thought to display a behavioral or developmental phenotype. Our study thus strengthens the evidence supporting the use of high dose sulfonylurea treatment in cases of K_{ATP}-related diabetes with any mutation, although a greater degree of benefit will likely be seen in patients with mutations that cause more significant neurodevelopmental impairment. As recognition of the importance of genetic testing in neonatal diabetes continues to grow, it is likely that babies will be identified and treated appropriately with sulfonylureas at an earlier age. Further long-term study of larger groups of patients at all ages and with all mutations subtypes will be required to better determine the extent to which any treatment benefits may depend on factors such as specific mutation, age at initiation of sulfonylureas, dose of sulfonylurea and/or extent of diabetes-related complications.

Our study has several limitations. There is no standardized tool available to assess neurodevelopment in those with *KCNJ11*-related NDM. The survey tool used in this study incorporated most questions from a standardized instrument but was further tailored specifically for concerns related to those with *KCNJ11*-related NDM. The survey instrument relied on parent or guardian report, as well as their willingness to participate, and was subject to sample bias. Although none of the subjects with transient neonatal diabetes responded (see above), we found that there were no differences between responders and non-responders with permanent neonatal diabetes. In addition, the sample obtained was representative of the distribution of mutations seen in the largest reports of *KCNJ11*-related NDM, with similar numbers of the most common mutations.[3,22] Although this study did not include full neuropsychological testing for the patients, the parent reports can be considered as reliable due to the presence of IEPs for two thirds of the patients with *KCNJ11*-related NDM. In order to more distinctly characterize the neurodevelopmental differences highlighted by our study, future research should be directed at performing neuropsychological testing in this population. To address a response bias, we used siblings as the control group. Future studies

should look at using a control group of individuals with other mutations that cause NDM in isolation, such as insulin gene mutations. The group of patients with *KCNJ11*-related NDM is difficult to compare to other individuals with diabetes, owing to the fact that they are treated with oral sulfonylureas rather than insulin and they do not regularly check their blood sugar.

Patients with *KCNJ11*-related NDM are at an increased risk for delays in learning, social-emotional and behavioral development. Additionally we have demonstrated that they have an increased risk for sleep disturbances and ADHD. Our comparison of patients with *KCNJ11*-related NDM to their unaffected sibling controls suggests that the neuropsychological impairments are associated with the K_{ATP} channel mutation rather than a familial genetic predisposition and lends support to the notion that K_{ATP} channel mutations in the brain independently affect neurodevelopment. Using the CBCL, Lord et al identified neurobehavioral dysfunction in a significant proportion of patients with congenital hyperinsulinism.[23] Their results indicated that in this group of children with glucose aberrations resulting from a rare genetic disease, identification of the neurocognitive deficits were not identified until academic problems occurred in school. Early identification, along with integrated medical and developmental support, may promote better neurodevelopmental outcomes for this unique population. We recommend a proactive multidisciplinary approach with involvement from the primary care physician, neuropsychologist, developmental and behavioral pediatrician and educators, in addition to the pediatric endocrinologist.

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Author contributions

K. L. drafted the initial manuscript, coordinated and supervised data collection, analyzed data and interpreted results. D. C. and M. L. wrote the manuscript, helped with data analysis, coordinated and supervised data collection and interpreted results. S. G. and M. M. wrote the manuscript, conceptualized and designed the study, coordinated and supervised data collection and supervised the study. All authors reviewed and revised the manuscript and approved the final manuscript as submitted.

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REFERENCES

1. Iafusco D, Massa O, Pasquino B, et al. Minimal incidence of neonatal/infancy onset diabetes in Italy is 1:90,000 live births. *Acta Diabetol*. 2012;49(5):405–408.
2. Slingerland AS, Shields BM, Flanagan SE, et al. Referral rates for diagnostic testing support an incidence of permanent neonatal diabetes in three European countries of at least 1 in 260,000 live births. *Diabetologia*. 2009;52(8):1683–1685.
3. Pearson ER, Flechtner I, Njølstad PR, et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. *N Engl J Med*. 2006;355(5):467–477.
4. De Franco E, Flanagan SE, Houghton JAL, et al. The effect of early, comprehensive genomic testing on clinical care in neonatal diabetes: and international cohort study. *The Lancet*. 2015;386(9997):957–963.
5. Rubio-Cabezas O, Hattersley AT, Njølstad PR, et al. The diagnosis and management of monogenic diabetes in children and adolescents. *Pediatr Diabetes*. 2014;15(S20):47–64.
6. Karschin C, Ecke C, Ashcroft FM, Karschin A. Overlapping distribution of K(ATP) channel-forming Kir6.2 subunit and the sulfonylurea receptor SUR1 in rodent brain. *FEBS Lett*. 1997;401(1):59–64.
7. Liss B, Bruns R, Roeper J. Alternative sulfonylurea receptor expression defines metabolic sensitivity of K-ATP channels in dopaminergic midbrain neurons. *EMBO J*. 1999;18(4):833–846.
8. Clark RH, McTaggart JS, Webster R, et al. Muscle dysfunction caused by a KATP channel mutation in neonatal diabetes is neuronal in origin. *Science*. 2010;329(5990):458–461.
9. Slingerland AS, Hurkx W, Noordam K, et al. Sulphonylurea therapy improves cognition in a patient with the V59M KCNJ11 mutation. *Diabet Med*. 2008;25(3):277–281.
10. Stoy J, Greeley SAW, Paz VP, et al. Diagnosis and treatment of neonatal diabetes: an United States experience. *Pediatr Diabetes*. 2008;9(5):450–459.
11. Busiah K, Drunat S, Vaivre-Douret L, et al. Neuropsychological dysfunction and developmental defects associated with genetic changes in infants with neonatal diabetes mellitus: a prospective cohort study. *Lancet Diabetes Endocrinol*. 2013;1(3):199–207.
12. Angriman M, Caravale B, Novelli L, Ferri R, Bruni O. Sleep in Children with neurodevelopmental disabilities. *Neuropediatrics*. 2015;46(03):199–210.
13. McDonough RJ, Clements MA, DeLurgio SA, Patton SR. Sleep duration and its impact on adherence in adolescents with type 1 diabetes mellitus. *Pediatr Diabetes*. 2016, DOI: 10.1111/pedi.12381.
14. Greeley SAW, Naylor RN, Cook LS, Tucker SE, Lipton RB, Philipson LH. Creation of the web-based University of Chicago Monogenic Diabetes Registry: using technology to facilitate longitudinal study of rare subtypes of diabetes. *J Diabetes Sci Technol*. 2011;5(4):879–886.
15. Biederman J, Monuteaux MC, Greene RW, Braaten E, Doyle AE, Faraone SV. Long-term stability of the child behavior checklist in a clinical sample of youth with attention deficit hyperactivity disorder. *J Clin Child Psychol*. 2001;30(4):492–502.
16. McCrimmon RJ, Ryan CM, Frier BM. Diabetes and cognitive dysfunction. *Lancet*. 2012;379(9833):2291–2299.
17. McTaggart JS, Clark RH, Ashcroft FM. The role of the KATP channel in glucose homeostasis in health and disease: more than meets the islet. *J Physiol*. 2010;588(17):3201–3209.
18. Shah RP, Spruyt K, Kragie BC, Greeley SAW, Msall ME. Visuomotor performance in KCNJ11-related neonatal diabetes is impaired in children with DEND-associated mutations and may be improved by early treatment with sulfonylureas. *Diabetes Care*. 2012;35(10):2086–2088.

19. McTaggart JS, Jenkinson N, Brittain JS, Greeley SAW, Hattersley AT, Ashcroft FM. Gain-of function mutations in the KATP channel (KCNJ11) impair coordinated hand-eye tracking. *PLoS One*. 2013;8(4):e62646.
20. Shaw M, Hodgkins P, Caci H, et al. A systematic review and analysis of long-term outcomes in attention deficit hyperactivity disorder: effects of treatment and non-treatment. *BMC Med*. 2012;10(1):99.
21. Thurber BW, Carmody D, Tadie EC, et al. Age at the time of sulfonylurea initiation influences treatment outcomes in *KCNJ11*-related neonatal diabetes. *Diabetologia*. 2015.
22. Slingerland AS, Nuboer R, Hadders-Algra M, Hattersley AT, Bruining GJ. Improved motor development and good long-term glycaemic control with sulfonylurea treatment in a patient with the syndrome of intermediate developmental delay, early-onset generalised epilepsy and neonatal diabetes associated with the V59M mutation in the KCNJ11 gene. *Diabetologia*. 2006;49(11):2559–2563.
23. Lord K, Radcliffe J, Gallagher PR, Adzick NS, Stanley CA, de León DD. High risk of diabetes and neurobehavioral deficits in individuals with surgically treated hyperinsulinism. *Clin Endocrinol Metab*. 2015;100(11):4133–9.

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