Title: Improved neurodevelopment following *in utero* sulfonylurea exposure in a patient with *KCNJ11* permanent neonatal diabetes: future implications for targeted treatment during pregnancy

Running title: Prenatal glyburide exposure in *KCNJ11* PNDM

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Twitter summary: Improved neurodevelopmental outcome after serendipitous exposure to glyburide *in utero* in a patient with *KCNJ11* neonatal diabetes: potential for future prenatal treatment of intellectual disability.

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Observation Letter

Neurodevelopmental and behavioural features represent the main challenge for many patients with permanent neonatal diabetes (PNDM) due to activating variants in the *KCNJ11* gene, encoding the Kir6.2 subunit of the ATP-sensitive potassium (K_{ATP}) channel. Individuals with the p.(Val59Met) *KCNJ11* variant have developmental delay, childhood onset generalised epilepsy and neonatal diabetes (intermediate DEND syndrome(1)). There are also high rates of autism spectrum disorder, attention deficits, hyperactivity, and impaired visuomotor performance(2,3). *KCNJ11*-PNDM can be treated with sulfonylureas, which bind to mutant K_{ATP} channels in the pancreas and restore functioning, allowing affected individuals to discontinue insulin. There is often a mild but incomplete improvement in neurological function after starting sulfonylureas suggesting that brain K_{ATP} channels respond in part to sulfonylureas(4).

Earlier sulfonylurea transfer may lead to better neurodevelopmental outcomes(3,4), likely due to increased neuronal plasticity in infancy. K_{ATP} channel dysfunction begins *in utero,* evidenced by low birth weights in *KCNJ11*-PNDM due to impaired fetal insulin secretion. Glyburide crosses the placenta and enters the fetal circulation(5), therefore it may be possible to target brain K_{ATP} channels at the earliest possible opportunity, via maternal glyburide treatment. Here, we describe the neurodevelopmental outcome in a patient with the p.(Val59Met) variant who, in addition to being treated early postnatally, was exposed to glyburide *in utero* due to treatment of maternal gestational diabetes.

The case, a 17-year-old female, was born at term weighing 2400g (Z-score -2.59). Her mother was diagnosed with gestational diabetes and serendipitously treated with glyburide 0.75mg/day from 10 weeks' gestation throughout pregnancy. At 6 weeks the patient presented with fever and raised CSF glucose. She was diagnosed with neonatal diabetes and started insulin therapy. This was switched to glyburide (titrating up to 1mg/kg/day) after two weeks, when genetic analysis identified a *de novo* heterozygous p.(Val59Met) pathogenic variant in the *KCNJ11* gene.

The parents of our case reported she had excellent speech development and was communicating in sentences at the expected age for this milestone. Her walking was delayed (27 months), and she had physiotherapy and occupational therapy from 13 months to 3 years. She developed complex partial seizures at 18 months, and was diagnosed with ADHD at 9 years. Her medications at that time comprised glyburide (8.75mg three times daily), oxcarbazepine (675mg daily), levetiracetam

(500mg daily), and atomoxetine. Anti-epileptic medication was stopped at 16 years and she has remained seizure-free.

Our case has attended age appropriate mainstream schooling since the age of 5 and will graduate with a diploma in general education this year. She has required some additional learning support particularly in Mathematics and English and her parents reported some challenges with visuospatial awareness, e.g. following directions. She played for the school soccer team, and is a competent cyclist.

The developmental trajectory described for this case contrasts with other p.(Val59Met) patients who have significant impairment requiring high levels of support and are unable to continue in mainstream schooling(1,2). This was demonstrated by the striking differences in the 'draw a man' task performed by our case aged 9 years, in comparison to adolescents or adults with the same p.(Val59Met) variant who started sulfonylurea treatment later (figure 1). It is unusual for a patient with this variant to have normal speech development, and to graduate from mainstream education with a view to independent living(1,2), as observed in our case. Her comparatively better developmental outcomes support the rationale for early sulfonylurea treatment, to target mutant K_{ATP} channels in the brain at a time of greater neuroplasticity. This concept is supported by a human induced pluripotent stem cell (hiPSC) organoid model expressing p.(Val59Met) which showed aberrant cortical neural network formation and reduced synchronisation in comparison to wild-type; abnormalities could be partly reversed with sulphonylurea (tolbutamide) treatment(6).

To date, this case is the only reported individual with the p.(Val59Met) variant known to have had exposure to glyburide *in utero*. Although the dose was relatively small, it is likely to have impacted brain K_{ATP} channels antenatally, in addition to the likely beneficial effect of early postnatal treatment. This is supported by research suggesting full scale IQ scores in patients with the p.(Val59Met) variant are usually in the moderate intellectual disability range even when glyburide is started 0-2 years postnatally(7). The potential to further improve outcome by treatment in pregnancy will become increasingly important as we offer non-invasive prenatal testing (NIPT) for pregnant mothers with K_{ATP} channel-related PNDM. NIPT affords an opportunity to identify affected fetuses early and, if the variant is maternally inherited or if the mother has gestational diabetes for another reason, provide targeted glyburide therapy via the affected mother to improve neurodevelopment(5). However, at present this remains speculative and formal research studies are needed to assess whether antenatal sulphonylurea therapy provides additional benefits to early

postnatal treatment, and if so what dose of glyburide is most effective for this purpose whilst maintaining safety and avoiding adverse events during pregnancy and in the neonatal period.

Importantly, our case had additional support in early childhood through physiotherapy, occupational therapy and specific educational interventions. She also received adjunctive pharmacological treatment with drugs that act in the brain. Future research is needed to dissect the relative contributions of genetic and non-genetic determinants of neurodevelopment in affected individuals, the factors affecting its variability, and how the timing of medical interventions can modify outcomes. This will enable further precision in our approach to treatment of neonatal diabetes.

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Guarantor statement

Dr Pamela Bowman takes full responsibility for the work as a whole, including the access to data, and the decision to submit and publish the manuscript.

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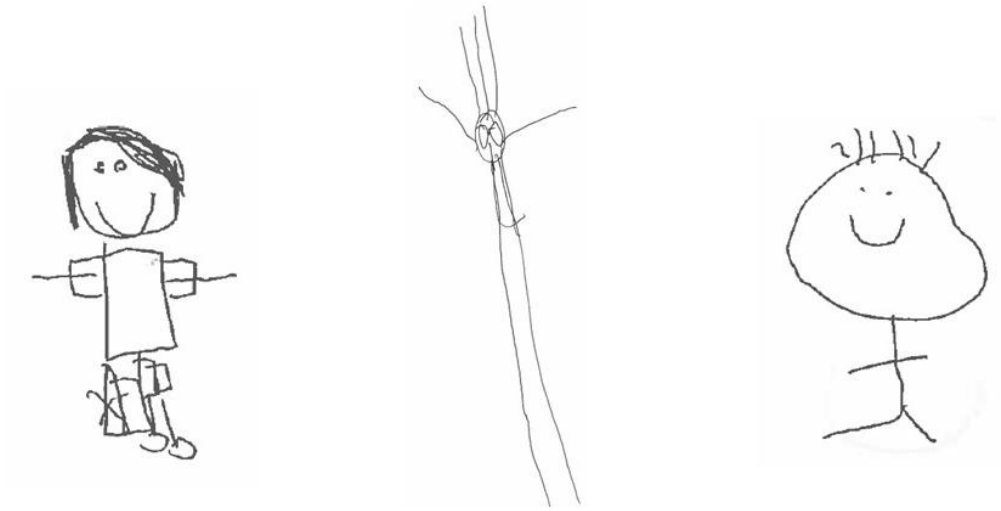
FIGURE LEGEND:

Figure 1 parts A, B, C. Draw a man task performed by case described and 2 other patients with the p.(Val59Met) *KCNJ11* variant, both older and transferred to sulfonylureas at a later age.



A. Case, aged 9 years
(SU *in utero*, SU treatment from 9 weeks)

B. V59M, aged 16 years
(SU treatment from 4 years)

C. V59M, aged 22 years
(SU treatment from 17 years)