Intellectual Disability in K_{ATP} Channel Neonatal Diabetes

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OBJECTIVE

Neonatal diabetes has been shown to be associated with high neuropsychiatric morbidity in a genotype-phenotype–dependent manner. However, the specific impact of different mutations on intellectual functioning is still insufficiently characterized. Specifically, only a small number of subjects with developmental delay have been comprehensively assessed, creating a knowledge gap about patients carrying the heaviest burden.

RESEARCH DESIGN AND METHODS

We assessed the intellectual functioning and mental health of the complete Norwegian population with K_{ATP} channel neonatal diabetes. Eight sulfonylurea-treated children (five with the p.V59M genotype [*KCNJ11*]) were assessed using age-matched control subjects with type 1 diabetes. The investigations included a physical and motor developmental examination, cerebral MRI, psychometrical examination, and questionnaires assessing intellectual capabilities and psychiatric morbidity.

RESULTS

A strong genotype-phenotype correlation was found, revealing the p.V59M genotype as highly associated with substantial intellectual disability, with no significant correlation with the time of sulfonylurea initiation. Consistent with previous studies, other genotypes were associated with minor cognitive impairment. Cerebral MRI verified normal brain anatomy in all but one child.

CONCLUSIONS

We here presented a comprehensive assessment of intellectual functioning in the largest cohort of p.V59M subjects to date. The level of intellectual disability revealed not only changes the interpretation of other psychological measures but downplays a strong protective effect of sulfonylurea. Within the scope of this study, we could not find evidence supporting an early treatment start to be beneficial, although a weaker effect cannot be ruled out.

Neonatal diabetes is most commonly caused by mutations in either of the two genes encoding the ATP-sensitive potassium channel (K_{ATP} channel): *KCNJ11* and *ABCC8* (1). Although patients can now appreciate a simplified treatment regimen, the general outlook is contrastingly somber. Recent studies have revealed a high prevalence of neurodevelopmental disorders in general (2–10), and some genotypes, like the p.V59M mutation, are at risk for severe neurological features due to its key position regarding the open probability of the channels (1,3,11).

The correlation of genotype with intellectual disability still remains to be fully characterized. To date, only a few studies have assessed intellectual functioning in

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these patients (4,7,8,10,12). However, the knowledge on intellectual functioning for the patients most affected is incomplete. This study addresses this knowledge gap.

RESEARCH DESIGN AND METHODS

Study Design and Patient Characteristics

The study was conducted in accordance with the latest version of the Declaration of Helsinki. The complete Norwegian cohort of subjects with K_{ATP} channel permanent neonatal diabetes was recruited by screening the Norwegian MODY (Maturity Onset Diabetes of the Young) Registry. Case subjects 1–6 were recruited in 2015 and assessed collectively during a week-long hospital stay. Case subjects 7 and 8 were included later and assessed individually with the same protocol. Children were examined in a fixed sequence in a cross-sectional manner. Parents reported on previous neurodevelopmental problems, aided by earlier neuropsychiatric assessments if available. Case subject 1 was reexamined because of a limited first assessment at first encounter. Control subjects were recruited from the outpatient clinic at the Department of Pediatrics and Adolescents at Haukeland University Hospital. Matching for age and disease duration was attempted but not fully achieved for the latter (mean 2.3 months [excluding case subject 7] vs. 3.6 years).

Neurodevelopmental Assessments and MRI

All subjects went through a clinical interview, a somatic and neurological examination, including a motor developmental assessment (the Danish Neurological Functioning Assessment or Bayley Scales of Infant and Toddler Development) (13,14). Furthermore, we performed MRI imaging of the brain (GE Discovery MR75 3.0 T). The protocol included a T1-weighted image, collected axially, using a fast-spoiled gradient recovery sequence (FSPGR BRAVO ARC) and a coronal T2-weighted volume sequence (CUBE). Three case subjects needed general anesthesia. Case subject 6 was imaged at the local hospital (1.5 T, T1-weighted MPRAGE collected sagittally, axial T2-weighted TSE, and T2-weighted FLAIR collected sagittally).

Psychological Assessments

An experienced children's neuropsychologist examined the intellectual functioning of the case group using the Wechsler Intelligence Scale for Children (WISC-IV) and a standardized clock drawing test. The WISC-IV is used in children and adolescents aged 6–16 years, providing a validated measure of intellectual functioning compared with Norwegian standardized norms (15,16). The Wechsler Preschool and Primary Scale of Intelligence (WPPSI), validated for younger children (17), was used for case subject 8. The clock drawing test measures visuospatial and graphomotor abilities, scored according to Norwegian standardized norms (18). The most recent ICD-11 classifies intellectual disability under disorders of intellectual development, defined as deficits in both intellectual and adaptive functioning two SDs below that of the general population (19).

Psychometric Questionnaires

Mental health was assessed with a compound questionnaire prepared for a previous mental health study (20). Parents completed the Strengths and Difficulties Questionnaire (SDQ) (revised version in the youngest subject); the Autism Spectrum Screening Questionnaire (ASSQ); the Swanson, Noland, and Pelham Questionnaire (SNAP-IV); the five-item version of Screen for Child Anxiety–Related Emotional Disorders (SCARED); and five obsessive-compulsive disorder (OCD) questions derived from the ICD (21–25). The questionnaires were largely complete and items were scored on a 3-point scale. SDQ is a validated behavioral screening questionnaire that generates scores for emotional symptoms, conduct problems, hyperactivity and inattention, peer problems, and prosocial behavior. Scoring is according to https://sdqinfo.org (25). ASSQ is a screening measure for autism spectrum disorder (23). SNAP-IV is a screening tool for attention deficit hyperactivity disorder (ADHD) (22).

Statistical Analyses

For the analyses of the psychometric questionnaires and tests and birth weight, we used an independent-sample Student *t* test to test for difference of means, assuming equal variances unless nonequality was indicated by Levene test. The nonparametric Mann-Whitney *U* test was used to test for differences of means in V59M carriers starting on sulfonylurea at different time points. For the comparison of the WISC-IV subtests, a paired-sample Student *t* test was used. A P value <0.05 was considered statistically significant.

RESULTS

Population

Eight unrelated children from different regions of Norway were included (Table 1). In our analyses, we split up the neonatal diabetes population into two groups: V59M (patients carrying the *KCNJ11* p.V59M mutation [$n = 5$]) and non-V59M *(KCNJ11,* p.F35V and p.F333I; and *ABCC8,* p.R1379H [$n = 3$]). The control subjects with type 1 diabetes are referred to as control subjects ($n = 5$). All subjects were born at term, and, unsurprisingly, neonatal diabetes was associated with lower birth weights (mean 2,976 vs. 3,823 g, $P < 0.0001$). The children were otherwise healthy, taking no medication other than glyburide, except methylphenidate for patients with ADHD. Sulfonylurea switch was from 4 months to 6 years of age. Pre- and postnatal periods were normal except for the admittance leading to the diagnosis of diabetes. None had a history of severe hypoglycemic episodes. Case subject 8 presented with a febrile seizure, leading to the discovery of ketoacidosis, and no seizures had been reported since. Case subject 2 was diagnosed with epilepsy after the assessments. All in the V59M group had either been diagnosed with mild intellectual disability or were suspected of developmental delay, but none were diagnosed with more severe intellectual disability. All subjects in the non-V59M group were diagnosed with ADHD. None of the control subjects reported any neuropsychiatric disorders.

Motor Developmental Assessment

None of the children had any apparent syndromic features, and no abnormalities were found during the routine examination except mild hypotonia in the youngest subject (case subject 8). All the V59M subjects displayed both fine and gross delayed motor development (Supplementary Table 1). Two of the three subjects in the non-V59M group demonstrated minor visuospatial problems but reported normal motoric development.

MRI

All subjects showed normal brain anatomy (Supplementary Table 2), but one subject displayed nonspecific signal abnormalities that were interpreted as

Table 1—Clinical characteristics of the study population

	Sex	Age (years)	GA (weeks)	BW (g) (perc.)	Genotype (gene; mutation)	Age debut diabetes (months)	Age SU switch (months)	Neuropsychiatric morbidity*	Medication	Dosage (mg/kg/day)	HbA_{1c} [mmol/mol (%)]
Case subjects											
1	Male	7	39	2,970 (10th–30th)	*KCNJ11;* p.V59M heterozygous	2	5	Diagnosed with mild intellectual disability	Glyburide	0.12	55 (7.2)
2	Female	11	40	2,540 (3rd–10th)	*KCNJ11;* p.V59M heterozygous	4	15	Diagnosed with mild intellectual disability	Glyburide	0.12	46 (6.4)
3	Male	11	39	3,260 (30th–50th)	*KCNJ11;* p.V59M heterozygous	1	14	Diagnosed with mild intellectual disability	Glyburide	0.13	39 (5.7)
4	Male	15	42	2,950 (3rd–10th)	*KCNJ11;* p.F35V heterozygous	1	62	Diagnosed with ADHD	Glyburide methylphenidate	0.15	49 (6.6)
5	Female	13	40	2,410 (<3rd)	*KCNJ11;* p.F333I heterozygous	2	27	Diagnosed with ADHD	Glyburide methylphenidate	0.26	60 (7.6)
6	Male	8	42	3,700 (>50th)	*KCNJ11;* p.V59M heterozygous	4	7	Suspected of developmental delay	Glyburide	0.14	39 (5.7)
7	Female	6	Unknown	Unknown	*ABCC8;* p.R1379H heterozygous	Unknown	78	Diagnosed with ADHD	Glyburide methylphenidate	0.06	40 (5.8)
8	Male	4	40	3,000 (30th–50th)	KCNJ11; p.V59M heterozygous	2	4	Diagnosed with global developmental delay	Glyburide	0.03	46 (6.4)
Control subjects											
1	Male	16	38	3,640 (>50th)	Type 1 diabetes	39	NA	None	Insulin	NA	NA
2	Male	8	41	4,500 (>50th)	Type 1 diabetes	48	NA	None	Insulin	NA	NA
3	Male	8	39	3,780 (>50th)	Type 1 diabetes	49	NA	None	Insulin	NA	NA
4	Female	10	41	3,995 (>50th)	Type 1 diabetes	10	NA	None	Insulin	NA	NA
5	Male	11	40	3,200 (30th–50th)	Type 1 diabetes	67	NA	None	Insulin	NA	NA

The case subjects were patients with permanent neonatal diabetes, and control subjects were patients with type 1 diabetes. All case subjects were carriers of heterozygous de novo mutations in the *KCNJ11* or *ABCC8* gene. Glyburide dosage is in mg/kg/day. BW, birth weight; GA, gestational age; SU, sulfonylurea. Percentiles (perc.) of birth weight are according to gestational age (35). NA, not applicable. *Recognized from before this assessment.

normal variation of the perivascular spaces (case subject 6).

Psychological Assessments

V59M was strongly associated with intellectual disability (Fig. 1), and all subjects displayed "moderate intellectual developmental disorder" (ICD-11). Case subject 8 received more help from parents than the instructions dictate, and the Full Scale Intelligence Quotient (FSIQ) score of 57 must therefore be treated as an overestimate. Despite this, his performance was clearly below the normal range. Compared with the non-V59M group, the V59M group showed not only significantly lower FSIQ (median 47 vs. 90, $P < 0.001$) but scored significantly lower on all subtests ($P < 0.001$) (Supplementary Table 3). The non-V59M group showed FSIQ scores within the normal range, but with a mean somewhat below the normal population (90 vs. 100). Furthermore, one subject displayed borderline intellectual dysfunction (Fig. 1). Intriguingly, all case subjects, regardless of genotype, scored significantly worse on nonverbal scales (perceptual reasoning index compared with verbal comprehension index [$P < 0.001$]) (Supplementary Table 4).

It has been suggested that starting sulfonylurea treatment early may alleviate the neurological features (8), but our results do not support this claim. All subjects with the high-risk genotype displayed the same level of intellectual disability regardless of their sulfonylurea treatment start, with no evidence of higher intellectual functioning in subjects switched early in life (Fig. 1 and Supplementary Table 5). A nonsignificant negative correlation could be demonstrated (Pearson correlation −0.727, $P < 0.164$), but this effect was mostly caused by the biased scores from case subject 8. After removal of this outlier, the effect was reduced but not absent (Pearson correlation −0.609, $P < 0.391$) (Supplementary Fig. 1). Even so, the large dependence of the correlation on small perturbations of a single individual indicates that the effect of early treatment, if it exists, is likely too small to be robustly captured with our small sample size. Therefore, to estimate the potential effect size, we used least squares regression assuming a linear relationship between the start of treatment and FSIQ (Supplementary Fig. 1). Although we cannot exclude a nonlinear effect, this revealed that the relationship is likely weak, with ~0.92 FSIQ points per month, which was further reduced to 0.46 if the outlier was removed.

The clock drawing test (Fig. 2) revealed a significant difference between the V59M and non-V59M groups ($P < 0.001$, Student t test). It also revealed that the majority in the non-V59M group performed the test with some difficulties. A correlation between the clock drawing test score and perceptual reasoning index was observed (Pearson correlation 0.943, $P < 0.001$) (Supplementary Fig. 2).

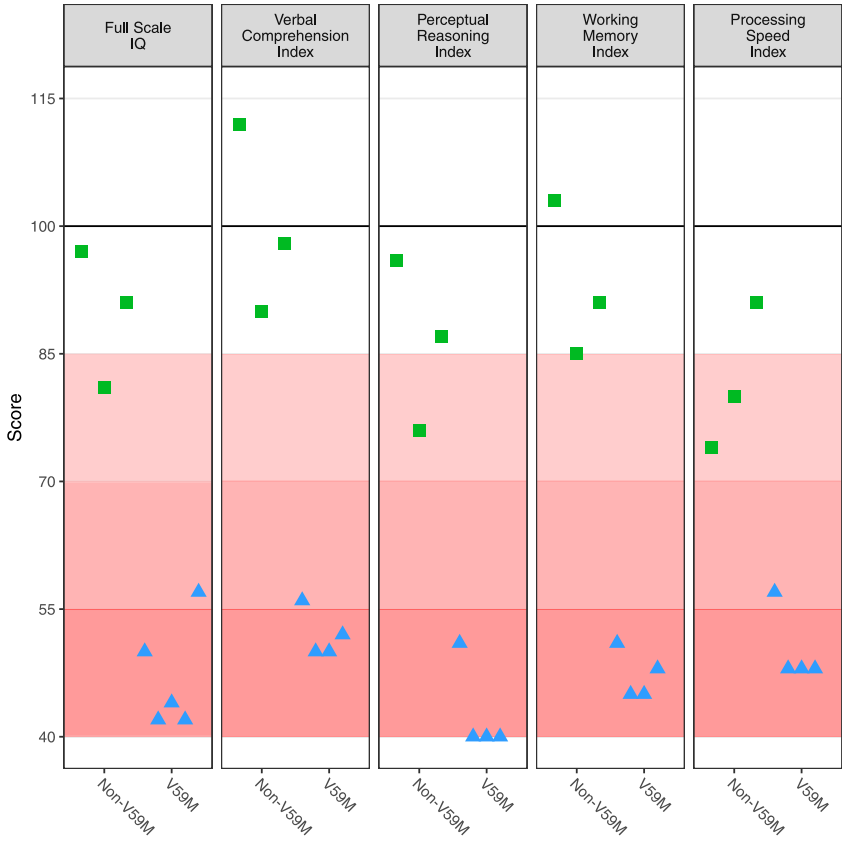

Figure 1—Intellectual functioning in the case subjects. Patients carrying the p.V59M genotype (blue triangles) showed moderate intellectual disability, most scoring in the lower range. For case subject 8, only a score for FSIQ is displayed (blue triangle at right margin). The three subjects from the non-V59M group (green squares) scored higher, but one did display borderline intellectual disability. Furthermore, all subjects showed significantly higher scores on verbal than nonverbal scales regardless of intellectual quotient, suggesting nonverbal learning disability.

Psychometric Questionnaires

The SDQ revealed high levels of psychopathology in the V59M group (Fig. 3 and Supplementary Table 6), with all subjects scoring in the abnormal range for the total difficulties score and significant differences in comparison with both the control subjects and the non-V59M group ($P < 0.001$ and $P < 0.017$). Similarly, significant differences were found between the V59M group and control subjects for scales measuring emotional disorders ($P < 0.012$), hyperactivity ($P < 0.001$), prosocial behavior ($P < 0.011$), and impact ($P < 0.001$). The non-V59M group scored higher than the control subjects but also displayed higher variance, and only conduct disorders yielded significant results ($P < 0.010$). Importantly, all patients in the non-V59M group were on symptom-suppressing medication, likely masking the true impact.

From the ASSQ (Fig. 4 and Supplementary Table 7), four subjects in the V59M group scored either in the borderline range or above the cutoff (>19). Overall, the score for the V59M group was significantly higher than the scores for the control subjects and the non-V59M group ($P < 0.001$ and $P < 0.012$).

In the screening assay for OCD (Supplementary Table 7), the V59M group confirmed compulsory behavior but not sufficient to diagnose OCD.

In SCARED (Supplementary Table 7), the V59M group scored significantly higher than the control subjects ($P < 0.012$), indicating a susceptibility toward anxiety disorders.

Finally, the SNAP inattention and the SNAP hyperactivity/impulsivity questionnaires showed significant differences between the V59M group and both the control subjects ($P < 0.001$ and $P < 0.003$) and the non-V59M ($P < 0.001$ and $P < 0.021$) group. Surprisingly, the non-V59M group scored low on these questionnaires, showing no difference from the control subjects (Supplementary

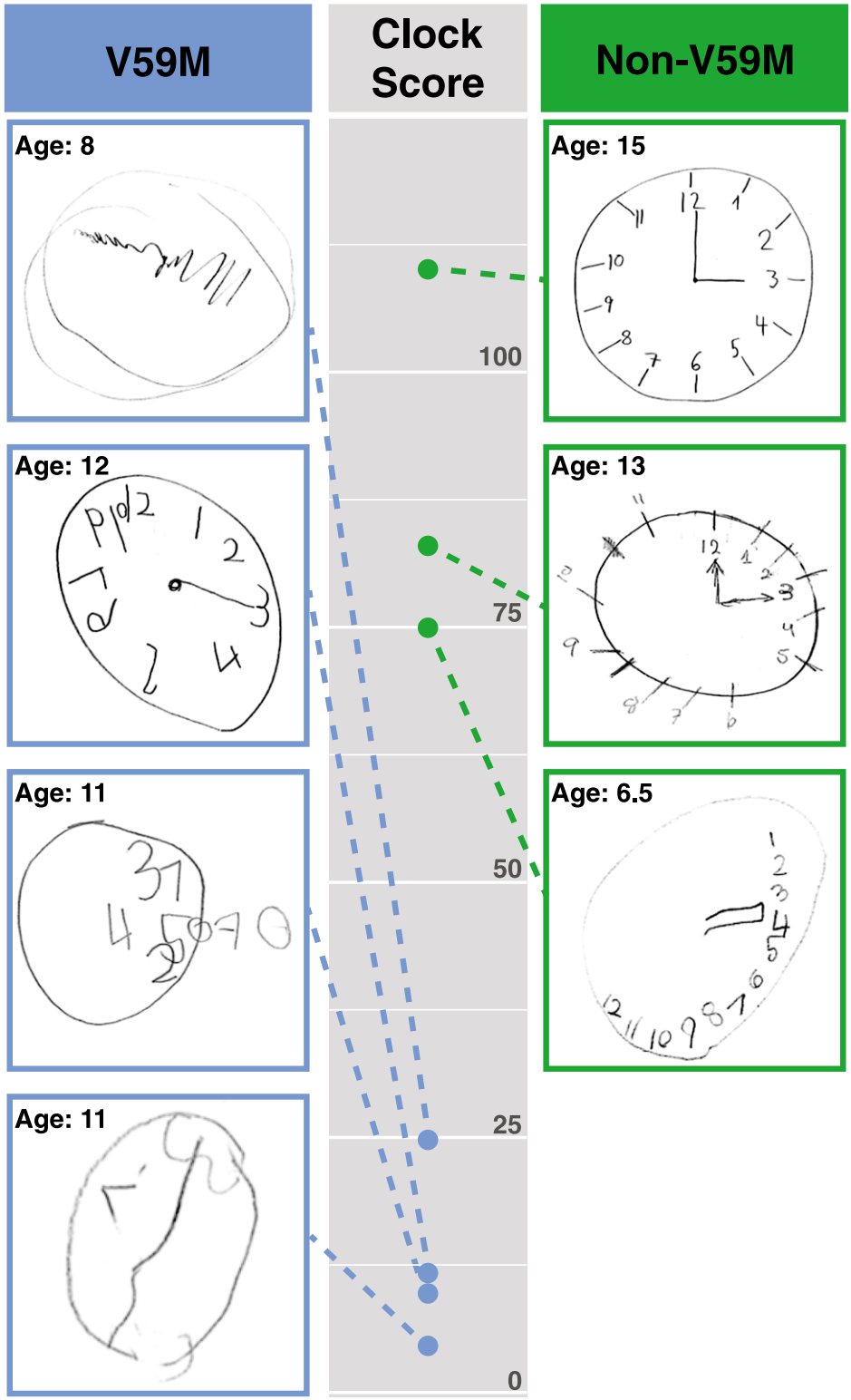

Figure 2—Clock drawing test scored in relation to the Norwegian normal population, with a mean of 100 and SD of 15. Patients with the p.V59M genotype scored in the lowest range, but two patients in the non-V59M group also displayed visuospatial deficits. Left, V59M (blue); right, non-V59M (green).

Table 7), potentially reflecting the symptom-relieving medication.

CONCLUSIONS

By examination, we demonstrated that patients with the V59M genotype show severe affection of cognitive abilities, collectively suffering from moderate intellectual disability. Although our sample size is small, the correlation between genotype and the severity of intellectual disability is highly significant. Importantly, the severity of intellectual disability complicates the interpretation of standard screening questionnaires, which must therefore be done with care.

Although data on intellectual disability are limited due to the rarity of the disorder and the challenges in assessing patients, our findings are consistent with previous studies. Bowman and colleagues (4,7) showed severe affection of cognitive abilities in two adult carriers of V59M switched late in life, and also reported severe developmental delay in four children treated with sulfonylurea since childhood. Similarly, Carmody et al. (10) found a mutation-dependent correlation between the p.V59M/p.V59A genotypes and developmental delay.

The neuroprotective effects of sulfonylurea have been extensively debated. Initially, case reports have both claimed and opposed an effect in children, but also improvement in motor functions was presented in an adult subject (26–31). To our knowledge, only two larger studies have suggested a positive effect of early treatment (8,12). The first, Beltrand et al. (8), reported an effect on motor functioning alone but no improvement of cognitive abilities. Importantly, the single subject with a severe genotype (V59M) did not show improvement in any of the end point measures. Furthermore, the conclusions on motor functioning have been challenged due to a heterogenous study population consisting mostly of less severe genotypes and a short follow-up (32). The second study, Shah et al. (12), demonstrated an inverse correlation between visuomotor functioning and onset of sulfonylurea. However, a caveat not previously discussed is the even stronger correlation observed with age that could reflect the test's inability to discriminate abnormal motor abilities in the youngest subjects (Pearson $r = -0.51$ [age] vs. $r = -0.45$ [sulfonylurea start]) (Supplementary Fig. 3). In light of these uncertainties, there is limited prior evidence supporting a neuroprotective effect.

The V59M subjects in this study were transferred to sulfonylurea in infancy or early childhood. Since all are still suffering from moderate intellectual disability with a strong genetic correlation, the benefits of early sulfonylurea treatment are likely to be limited. Moreover, we find no evidence that an earlier start is advantageous within the span of our subjects. This is supported by the results from our recent 10-year follow-up study in a significantly larger cohort ($n = 91$), revealing persistent neurological features (5). Studies showing that sulfonylurea is restricted by the blood-brain barrier and actively transported out of the brain could explain why we failed to find a neuroprotective effect (33). Of note, the current study cannot answer if a very early treatment start (shortly after birth) can be beneficial. We cannot completely rule out that the outcome for these patients would be even worse in the absence of sulfonylurea since the Norwegian MODY Registry includes no subjects switched to sulfonylurea later in life for comparison.

Nonspecific MRI findings have previously been described in neonatal diabetes, with reports of abnormal findings in the majority of patients in a single study (8). Surprisingly, our cohort displayed normal cerebral MRI from all subjects. A difference is that these subjects had been switched early in life (mean 26.5 months vs. median 5 years [range 0.1–18.5]), which could indicate a possible protective mechanism of sulfonylurea. However, a more recent study also presented no structural abnormalities in subjects switched later (mean age 21.1 years), arguing that intellectual disability is primarily due to functional abnormalities. Due to the small sample sizes in all these studies, this leaves the question open as to whether abnormalities in the brain are overrepresented.

For patients with less severe K_{ATP} channel dysfunction (the non-V59M group), this study could only obtain three subjects, so strong conclusions cannot be drawn.

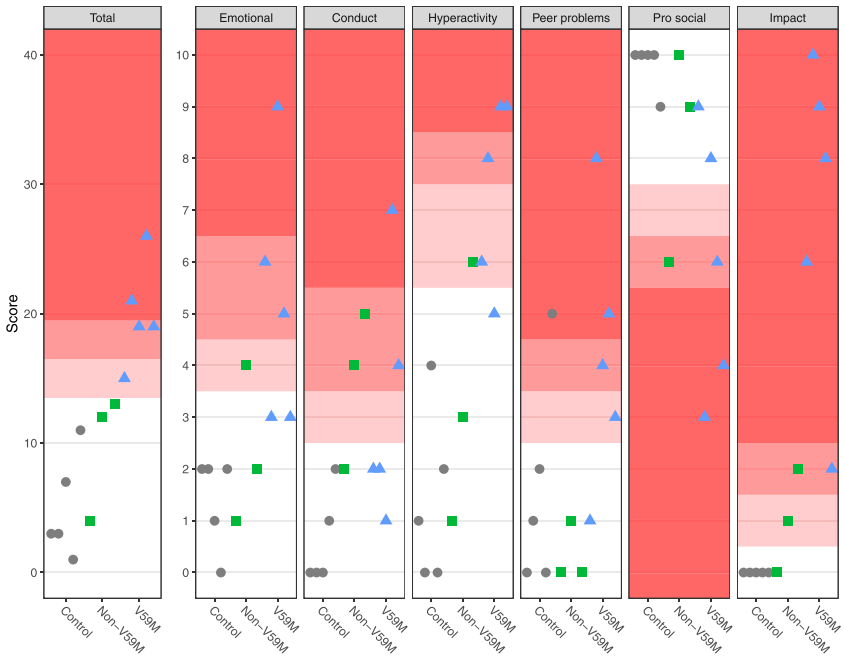

Figure 3—The SDQ results. The V59M group shows high levels of psychiatric morbidity with significantly elevated scores on all scales, including the total difficulties and impact scores, but the level of intellectual disability renders the questionnaires invalid. The non-V59M group reveals more problematic behavior on several scales but fails in reaching statistical significance. Total (total difficulties score) is a summation of conduct disorders, emotional disorders, hyperactivity, and peer problems. Case subject 8 submitted the version aimed at 2–4 year olds, with a lower cutoff for pathology. For simplicity, no correction factor has been used in the figure. Control (gray circles), control subjects with type 1 diabetes; non-V59M (green squares), subjects with mutations other than *KCNJ11* p.V59M; V59M (blue triangles), patients with the *KCNJ11* p.V59M mutation.

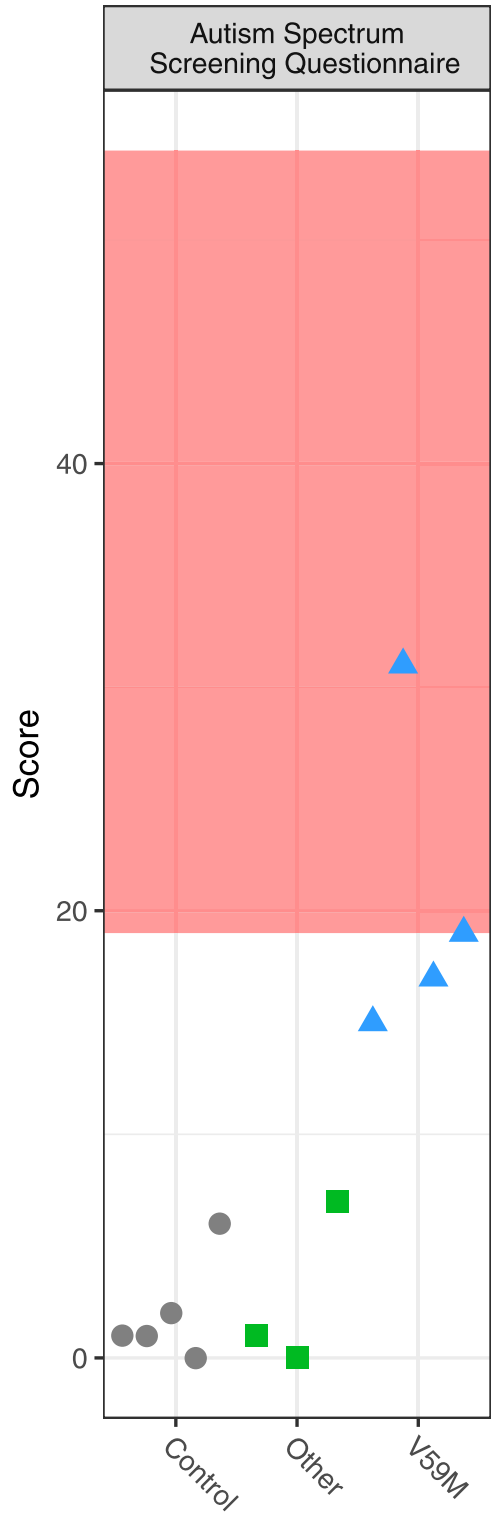

Figure 4—Overview of ASSQ results. One V59M subject scored above the cutoff and three in the borderline range. Non-V59M and control subjects did not show pathology. Control (gray circles), control subjects with type 1 diabetes; non-V59M (green squares); case subjects with mutations other than *KCNJ11* p.V59M; V59M (blue triangles), case subjects with the *KCNJ11* p.V59M genotype.

Even so, similar to other studies, we demonstrated less pronounced cognitive impairment (4,6,7,10) and also found a high prevalence of ADHD (2,6,34), which might reflect unrecognized cognitive impairment or that they exhibit both these features.

In conclusion, our study shows that carriers of the p.V59M mutation are affected by moderate intellectual disability. These subjects report symptoms of a spectrum of neuropsychiatric disorders, but the underlying cause can be explained by the severity of intellectual disability. Furthermore, our results indicate that if sulfonylurea has a beneficial effect on the brain, it cannot be fully protective. Even so, our patients and their families were clearly underrecognized, adding comorbidity to the disorder. This demonstrates that a cross-disciplinary approach is crucial to comprehend the full spectrum of challenges faced by patients. Reaching this goal is essential to achieve optimal and personalized care for this complex patient group.

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Duality of Interest. P.S. received standard compensation for a scientific talk held on the topic of monogenic diabetes at the AstraZeneca-hosted Nordic/Baltic Diabetes Science Forum in January 2019. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. P.S., J.R.F., I.B.E., and P.R.N. designed the study. P.S. and Å.S. collected data. P.S. and H.I. performed the clinical examinations. J.R.F. performed the neuropsychological tests. S.M.A. performed the MRI interpretations. E.S. contributed to MRI assessments. P.S. analyzed the data and performed the statistical analyses, with contributions from S.K.E.F. and E.V. P.S., E.V., and P.R.N. wrote the manuscript. P.R.N. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. A summary of the preliminary results was presented at the Nordic/Baltic Diabetes Science Forum, 30 January–2 February 2019, Gothenburg, Sweden, where P.S. was an invited speaker, and in a poster session at the Norwegian Diabetes Research Forum, 2–4 April 2019, Oslo, Norway. An abstract and poster of the preliminary results were presented at the 55th Annual Meeting of the European Association for the Study of Diabetes, Barcelona, Spain, 16–20 September 2019, and the 45th Annual Conference of the International Society for Pediatric and Adolescent Diabetes (ISPAD), Boston, MA, 30 October–2 November 2019 (by P.S.), and invited talks reporting part of the data were presented at the 58th Annual Meeting of the European Society for Paediatric Endocrinology,

Vienna, Austria, 19–21 September 2019, and the 45th Annual Conference of ISPAD (by P.R.N.).

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