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Prospective Multicenter Validation of a Simple Blood Test for the Diagnosis of Glut1 Deficiency Syndrome

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Study Question

Is METAglut1 a robust test for the diagnosis of Glut1 deficiency syndrome?

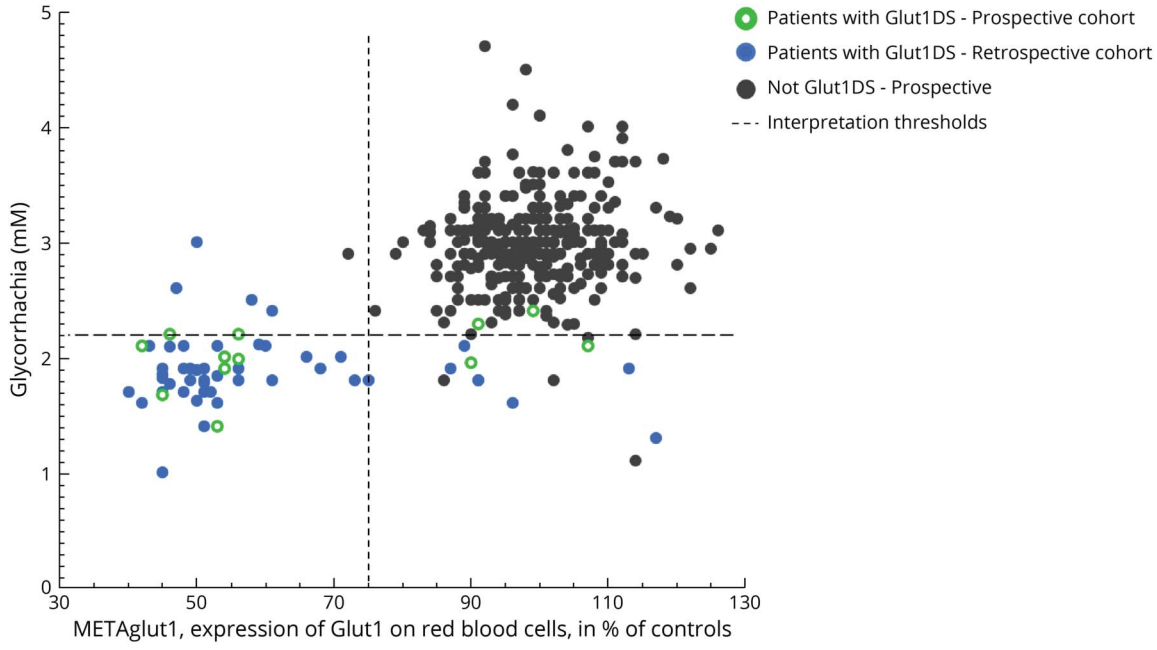
What Is Known and What This Paper Adds

GLUT1 deficiency syndrome (Glut1DS) is a treatable neurometabolic disease caused by glucose transporter 1 impairment, which induces a wide range of neurologic symptoms in children and adults. Its diagnosis relies on a lumbar puncture (LP) to measure glycorrhachia and sometimes complex molecular analyses of the *SLC2A1* gene. This procedure limits the number of patients able to receive the standard of care. Moreover, the early detection of Glut1DS is critical because the disease is treatable with ketogenic diets or novel experimental therapies. METAglut1 is a blood test relying on the quantification of GLUT1 at the erythrocyte surface for the early detection of Glut1DS. The results of this study show that METAglut1 was 80% sensitive and >99% specific for the diagnosis of Glut1DS and thus provide Class I evidence that a positive METAglut1 test accurately distinguishes patients with Glut1DS from other neurologic syndromes when compared with invasive and genetic testing.

Methods

We performed a multicenter validation study in France involving 33 hospitals. We studied 2 patient cohorts including both children and adults. A prospective cohort included patients with a clinical suspicion of Glut1DS, presenting with intellectual disability or mixed specific neurodevelopmental disorder, and/or epilepsy, and/or permanent or paroxysmal movement disorders; patients were explored through the reference strategy, that is, LP and analyses of the *SLC2A1*

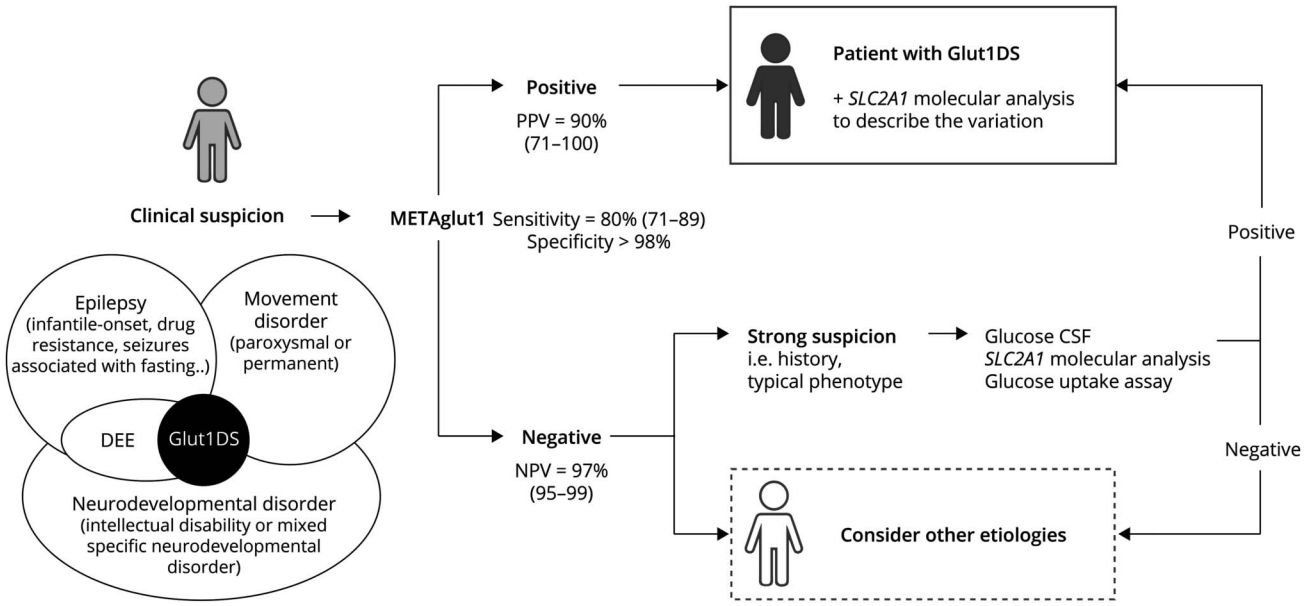
Figure 1 Concordance Analysis



Prospective cohort only	k = 0.59 CI_{95} (0.33 – 0.85)
Prospective + retrospective cohort	k = 0.78 CI_{95} (0.69 – 0.87)

The recommended interpretation thresholds are represented with dashed lines at 2.2 mM (40 mg/dL) for glycorrhachia and 76% of normal expression for METAglut1.

Figure 2 Proposed New Diagnostic Algorithm



DEE = developmental and epileptic encephalopathy; Glut1DS = Glut1 deficiency syndrome; NPV = negative predictive value; PPV = positive predictive value; Se = sensitivity; Spe = specificity.

gene. A retrospective cohort included patients previously diagnosed with Glut1DS. Clinical data, glycorrhachia measurement, and molecular analysis were collected through an electronic case report form, and all patients were blind tested with METAglut1. We performed concordance analyses between METAglut1 and glycorrhachia and analyzed the diagnostic performances of METAglut1, that is, sensitivity, specificity, and positive and negative predictive values.

Results

We analyzed 428 patients in the prospective cohort (mean age 12 years, SD 13, 46% female), including 15 patients newly diagnosed with Glut1DS, and 67 patients in the retrospective cohort (mean age 13 years, SD 13, 49% female). METAglut1 and glycorrhachia were in agreement, with a Cohen κ coefficient of 0.59 (0.33–0.85) on the prospective cohort and 0.78 (0.69–0.87) on the overall (prospective and retrospective) cohort, which is considered as a substantial agreement (Figure 1). METAglut1 sensitivity was found to be 85% (95% CI 76–94) in the retrospective cohort of 60 index patients with Glut1DS. Sensitivity in the prospective group of 205 patients, including 15 index patients with Glut1DS, was 60% (35–85). Specificity reached 99% (98–100), and positive and negative predictive values were 90% (71–100) and 97% (95–99), respectively. Overall, METAglut1 was 80% sensitive and >99% specific for the diagnosis of Glut1DS. The main limitation of this study is that the reference strategy was not available for all patients. To tackle underdiagnosis and medical wandering, we suggest to perform METAglut1 in any patient who presents with a clinical suspicion of Glut1DS (Figure 2).

Registration, Study Funding, and Competing Interests

This study was registered under Clinical Trial registration number NCT03722212. This study was supported by French Health Authorities, that is, the *Forfait Innovation*, and funded from the European Union's Horizon 2020 research and innovation program. Some authors report competing interests. Go to Neurology.org/N for full disclosures.

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