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Child Neurology: Differential diagnosis of a low CSF glucose in children and young adults

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ABSTRACT

Analysis of CSF is daily routine in patients with acute neurologic disorders like CNS infections. In those patients, the finding of a low CSF glucose may influence further diagnostic workup and therapeutic choices. The interpretation of a low CSF glucose in patients with a chronic neurologic disorder, however, is a less common practice. We present a practical overview on the differential diagnosis of a low CSF glucose and stress the importance of recognizing a low CSF glucose as the diagnostic marker for GLUT1 deficiency syndrome, a treatable neurometabolic disorder. ***Neurology*® 2013;81:e178–e181**

GLOSSARY

GLUT1DS = GLUT1 deficiency syndrome.

Analysis of CSF is routine in patients with acute neurologic disorders like CNS infections. In those patients, the finding of a low CSF glucose (i.e., hypoglycorrhachia) can be decisive for further diagnostic and therapeutic management. In patients with a chronic neurologic disorder like intellectual disability or epilepsy, however, a low CSF glucose is easily overlooked, especially when other CSF parameters are normal.[1] A low CSF glucose, though, is the diagnostic clue for GLUT1 deficiency syndrome (GLUT1DS), a treatable neurometabolic disorder.[2]

To develop a flow chart for the differential diagnosis of a low CSF glucose in neurologic disorders in children and young adults, we performed a literature search on Pubmed by using MeSH terms (CSF, glucose, CNS infections, CNS diseases) with subheadings (CSF, diagnosis), as well as free search terms such as GLUT1 deficiency syndrome, posthemorrhagic hydrocephalus, and ventriculoperitoneal shunt. Little is known, however, about the differential diagnosis of a low CSF glucose in the absence of an elevated cell count or elevated CSF lactate level (further referred to as "isolated low CSF glucose"). Therefore, we additionally performed a retrospective search in our CSF database[3] for CSF samples of patients younger than 21 years of age with an isolated low CSF glucose (figure 1).

RETROSPECTIVE SEARCH FOR PATIENTS WITH AN ISOLATED LOW CSF GLUCOSE Between 1993 and 2008, the results of all CSF samples that were analyzed at the laboratory of our tertiary referral hospital (the Radboud University Medical Centre in Nijmegen, the Netherlands) were systematically collected.[3] Out of 10,193 CSF samples of patients younger than 21 years of age, we identified 68 samples (0.7%) of 64 unique patients with an isolated low CSF glucose (for inclusion and exclusion criteria see figure e-1 on the *Neurology*® Web site at www.neurology.org). For methods, we refer to Leen et al.[3] Medical records of these patients were evaluated (according to the regulations of the local Medical Ethical Committee, METC Arnhem-Nijmegen) (table e-1). Two patients were already diagnosed with GLUT1DS. Twelve patients were retrospectively clinically suspected of GLUT1DS because of intellectual disability, epilepsy, or movement disorders, and the absence of another final diagnosis. We were able to contact 11 patients and/or caregivers, and a lumbar puncture was repeated in 5 patients, revealing a normal CSF glucose in 4 patients. In the patient with the repeated low CSF

Supplemental data at www.neurology.org

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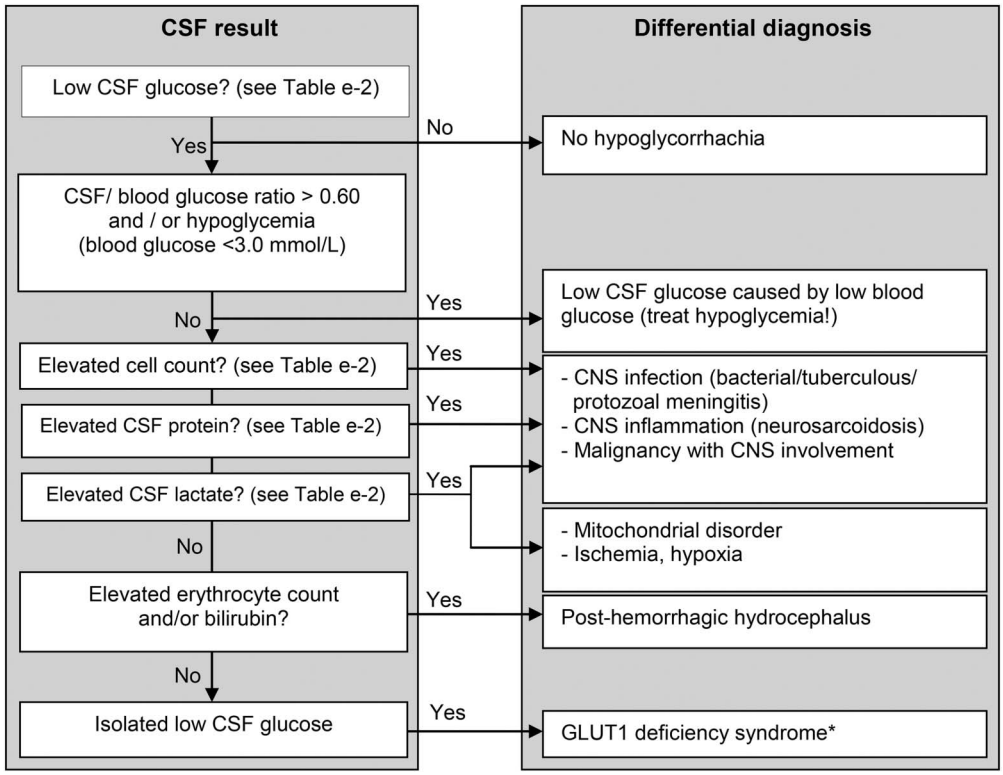
Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Figure 1 Flow chart for the differential diagnosis of a low CSF glucose



*An isolated low CSF glucose can be a coincidental finding in other neurologic disorders (see table e-1).

glucose, as well as in the remaining 6 patients without permission for repetition of lumbar puncture, *SLC2A1* mutation analysis was performed. An *SLC2A1* mutation was revealed in one of the 6 patients without a repeated lumbar puncture (described in the case report below).

CASE REPORT A 27-year-old man was known at our department of neurology with a history of intellectual disability, epilepsy, and movement disorders. He had complex partial seizures since the age of 8 months and sporadic tonic-clonic seizures, for which he had been treated with several antiepileptic drugs with moderate effect. Since the age of 10 years he had experienced cerebellar ataxia and action myoclonus. Extensive and repeated metabolic investigations in CSF, blood, and urine, as well as neuroimaging, had revealed no abnormalities. An etiologic diagnosis had not been made.

Our retrospective search for CSF samples with an isolated low CSF glucose, however, revealed a CSF glucose of 1.9 mmol/L (ref: 2.7–4.4 mmol/L) and a CSF/blood glucose ratio of 0.51 (ref: 0.46–0.90) in this patient at the age of 20 years, in combination with a normal cell count of 3/μL (ref: <5 μL), a normal total protein concentration of 492 mg/L (ref: <500 mg/L), and a low CSF lactate of 0.99 mmol/L (ref: 1.2–2.2 mmol/L). Because of a high suspicion of GLUT1DS, *SLC2A1* mutation analysis was performed, which showed a pathogenic heterozygous mutation (c.136C > T; p.Gln46X). A modified Atkins diet was initiated at the age of 29 years, with notable reduction of the seizures, dysarthria, ataxia, and action myoclonus, as well as improvement of alertness and cognitive function, according to the caregivers.

DISCUSSION The differential diagnosis of a low CSF glucose strongly depends on the clinical symptomatology, as well as the results of other CSF parameters, CSF cultures, and neuroimaging. CSF glucose, however, can be of additional value or even lead to the correct diagnosis. Little consensus exists among laboratories about the reference values for CSF glucose. CSF glucose is mostly referred to as being abnormal below 2.2 or 2.5 mmol/L, for which no scientific proof exists. Requirements for a correct interpretation of CSF glucose, however, include the use of age-specific reference values[3] (table e-2) and parallel analysis of blood glucose to calculate the CSF/blood glucose ratio, which should be taken before the lumbar puncture to avoid stress-induced hyperglycemia and thereby a false-positive low CSF/blood glucose ratio.

If a low CSF glucose is found in combination with a CSF/blood glucose ratio >0.60, hypoglycemia is

the cause of the low CSF glucose. In our database we identified 11 out of 10,193 children (0.1%), all younger than 5 years of age, with hypoglycemia (defined as blood glucose <3.0 mmol/L) at the moment of the lumbar puncture. In young children, a lumbar puncture is often performed under anesthesia, and physicians should be alert for hypoglycemia during the procedure.

A low CSF glucose is found in patients with bacterial, tuberculous, fungal, and protozoal meningitis, almost always in combination with other abnormal CSF parameters. In patients with bacterial meningitis, CSF glucose is generally decreased in combination with a strong polynuclear pleocytosis and increased CSF total protein and lactate levels. This is in contrast to an only moderately elevated and predominantly mononuclear cell count and normal or only slightly increased total protein level in viral meningitis.[4] A low CSF glucose is rare in viral CNS infections, but moderate hypoglycorrhachia may occur in viral CNS infections due to mumps virus, enterovirus, and herpes simplex virus 1. In the vast majority of children with tuberculous, fungal, and protozoal meningitis, CSF glucose is decreased in combination with a moderate mononuclear pleocytosis with lymphocytic predominance and a strongly elevated protein and lactate concentration.[5] In patients with an isolated low CSF glucose, CNS infection is very unlikely but not totally ruled out: in our database we identified one child with a mycoplasma infection with low CSF glucose with other normal CSF parameters (table e-1).

A low CSF glucose can also be found in relation to CNS inflammation, including neurosarcoidosis and leptomeningeal metastasis. The most consistent CSF abnormalities in these disorders are an elevated total protein concentration and lactate value.[6] Furthermore, a low CSF glucose in combination with a normal cell count and protein concentration but with an elevated CSF lactate can be found in mitochondrial disorders[7] or after cerebral ischemia or hypoxia.

While leukocyte count, total protein concentration, and glucose are routinely investigated, CSF lactate is often not taken into account in the diagnostic workup of CNS infections.[4,5] CSF lactate, however, is of additional value in the differentiation between bacterial, viral, and tuberculous meningitis,[8] which is important because in the majority of clinically suspected cases bacterial CSF cultures remain negative if the lumbar puncture is performed after initiation of antibiotic treatment. CSF lactate is in general strongly elevated in bacterial, tuberculous, and protozoal meningitis, whereas normal or only slightly elevated CSF lactate values are found in viral meningitis.

A low CSF glucose can also be found in posthemorrhagic hydrocephalus, mostly in combination with an elevated erythrocyte count and bilirubin concentration.[9] This appears to reflect a common phenomenon and does not necessarily indicate a CNS infection. Posthemorrhagic hydrocephalus was present in a few patients with an isolated low CSF glucose in our database, which indicates that low CSF glucose may persist even after erythrocyte and bilirubin concentrations have already diminished.

A low CSF glucose in combination with a normal cell count, a normal protein level, and a low to normal CSF lactate is the diagnostic marker for GLUT1DS, a genetic neurometabolic disorder in which glucose transport into the brain is disturbed.[2] The clinical phenotype of GLUT1DS is large and includes intellectual disability in combination with epilepsy and movement disorders, early-onset absence epilepsy, and paroxysmal exertion-induced dystonia. The incidence of GLUT1DS is estimated at 2.6 in 1,000,000,[10] but this is probably an underestimation since diagnosis is easily missed.[1] Diagnosis is based on the clinical symptoms in combination with a typical GLUT1DS CSF profile, i.e., low CSF glucose (range 0.9–2.7 mmol/L) in combination with a CSF/blood glucose ratio below 0.60 and CSF lactate below or within normal range, in contrast to mostly an elevated CSF lactate in CNS infection or inflammation. Cerebral imaging generally does not show structural abnormalities. GLUT1DS can be treated with a ketogenic diet, which provides the brain with an alternative energy source. Diagnosis of GLUT1DS can be confirmed by mutation analysis of the *SLC2A1* gene. Most patients with GLUT1DS have de novo mutations, but autosomal dominant inheritance in families with a mild phenotype is found as well. Genotype-phenotype correlations have been noted, with missense mutations being associated with milder phenotypes. The phenotypic variability between patients with the exact same mutation is large, however, which should be taken into account with genetic counseling. It is important to realize that no *SLC2A1* mutation is found in about 10% of all patients with the clinical picture and CSF profile of GLUT1DS. This may hint at other yet unknown genetic causes leading to a glucose deficit in the CNS. Diagnosis of probable GLUT1DS is then based on clinical symptoms and CSF results. It is important to recognize these patients since they can be treated with a ketogenic diet.

The differential diagnosis of an isolated low CSF glucose besides GLUT1DS is relatively small. Out of 64 patients with a low CSF glucose in our CSF database, 14 patients (22%) were diagnosed with a (possible) glucose transport disorder, and in the remaining 50 patients (78%) a low CSF glucose was a coincidental finding in other neurologic disorders (table e-1). Reversible isolated low CSF glucose has been described in infants with seizures during the first months of life and is thought to represent a benign condition with a transient disturbance of

GLUT1-mediated glucose transport. Furthermore, apparent artificial low CSF glucose within ventriculoperitoneal shunt systems sometimes causes confusion and GLUT1DS is suspected. This phenomenon has not been evaluated in the literature and seems unrelated to CSF infection or raised intracranial pressure. Workup for GLUT1DS in these patients is only warranted if the condition is suspected on clinical grounds and low CSF glucose was determined by means of a lumbar puncture. In addition, an isolated low CSF glucose was found in our database in a few patients with mitochondrial disorders. In most patients with a mitochondrial disorder, however, CSF lactate is elevated and results of other diagnostic tests such as muscle biopsy will lead to the correct diagnosis.

In summary, a low CSF glucose is an important diagnostic clue in acute as well as chronic neurologic disorders. An isolated low CSF glucose in combination with a low to normal CSF lactate is the diagnostic marker for GLUT1DS and should not be missed.

AUTHOR CONTRIBUTIONS

All coauthors were involved in drafting and/or revising of the article for intellectual content. W.G. Leen: study concept and design, literature research, analysis and interpretation, drafting and revising the manuscript for intellectual content. C.J. de Wit: acquisition of data and critical revision of the manuscript for intellectual content. R.A. Wevers: critical revision of the manuscript for important intellectual content. B.P. van Engelen: study concept and critical revision of the manuscript for important intellectual content. E.J. Kamsteeg: critical revision of the manuscript for important intellectual content. J. Klepper: critical revision of the manuscript for important intellectual content. M. Verbeek: acquisition of data, analysis and interpretation, revising the manuscript for intellectual content. M.A. Willemsen: study concept and design, analysis and interpretation, revising the manuscript for important intellectual content.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

W. Leen received a research grant for working on the subject of glucose transport in the brain (The Netherlands Organization for Scientific Research; Project number 92003529) C.J. de Wit reports no disclosures. R. Wevers reports no disclosures. B. van Engelen reports no disclosures. E. Kamsteeg reports no disclosures. J. Klepper reports no disclosures. M. Verbeek is a consultant for Schering Plough Research Institute and received a research grant from the Dutch Foundation Stichting, Stichting Internationaal Parkinson Fonds, Van Alkemade Keuls Fonds, AADC Research Trust, and Center for Translational Molecular Medicine. M. Willemsen reports no disclosures. Go to Neurology.org for full disclosures.

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Neurology 2013;81;e178-e181
DOI 10.1212/01.wnl.0000437294.20817.99