TABLE 4 Common Recognizable XLID Syndromes

Syndrome	Common Manifestations	Gene, Location
Aarskog syndrome	Short stature, hypertelorism, downslanting palpebral fissures, joint hyperextensibility, shawl scrotum	*FGD1,* Xp11.21
Adrenoleukodystrophy	Variable and progressive vision and hearing loss, spasticity, neurological deterioration associated with demyelination of the central nervous system and adrenal insufficiency	*ABCD1,* Xq28
Aicardi syndrome	Agenesis of the corpus callosum, lacunar chorioretinopathy, costovertebral anomalies, seizures in females	_____, Xp22
Allan–Herndon syndrome	Generalized muscle hypoplasia, childhood hypotonia, ataxia, athetosis, dysarthria, progressing to spastic paraplegia	*MCT8* (SLC16A2), Xq13
ARX-related syndromes (includes Partington, Proud, West, XLAG syndromes and nonsyndromal XLMR)	Partington: dysarthria, dystonia, hyperreflexia, seizures. West: infantile spasms, hypsarrhythmia. Proud: microcephaly, ACC, spasticity, seizures, ataxia, genital anomalies. XLAG: lissencephaly, seizures, genital anomalies	*ARX,* Xp22.3
ATRX syndrome (includes ARTX, Chudley–Lowry, Carpenter–Waziri, Holmes–Gang, and Martinez spastic paraplegia syndromes and nonsyndromal XLMR)	Short stature, microcephaly, hypotonic facies with hypertelorism, small nose, open mouth and prominent lips, brachydactyly, genital anomalies, hypotonia, in some cases hemoglobin H inclusions in erythrocytes	*XNP,* (XH2) Xq13.3
Christianson syndrome	Short stature, microcephaly, long narrow face, large ears, long straight nose, prominent mandible, general asthenia, narrow chest, long thin digits, adducted thumbs, contractures, seizures, autistic features, truncal ataxia, ophthalmoplegia, mutism, incontinence, hypoplasia of the cerebellum, and brain stem	*SLC9A6,* Xq26
Coffin–Lowry syndrome	Short stature, distinctive facies, large soft hands, hypotonia, joint hyperextensibility, skeletal changes	*RSK2,* Xp22
Creatine transporter deficiency	Nondysmorphic, autistic, possibly progressive	*SLC6A8,* Xq28
Duchenne muscular dystrophy	Pseudohypertrophic muscular dystrophy	*DMD,* Xp21.3
Fragile X syndrome	Prominent forehead, long face, recessed midface, large ears, prominent mandible, macroorchidism	*FMR1,* Xq27.3
Hunter syndrome	Progressive coarsening of face, thick skin, cardiac valve disease, joint stiffening, dysostosis multiplex	*IDS,* Xq28
Incontinentia pigmenti	Sequence of cutaneous blistering, verrucous thickening, and irregular pigmentation. May have associated CNS, ocular abnormalities	*NEMO* (IKB6KG), Xq28
Lesch–Nyhan syndrome	Choreoathetosis, spasticity, seizures, self-mutilation, uric acid urinary stones	*HPRT,* Xq26
Lowe syndrome	Short stature, cataracts, hypotonia, renal tubular dysfunction	*OCRL,* Xq26.1
MECP2 duplication syndrome	Hypotonia, progressing to spastic paraplegia, recurrent infections	*MECP2,* Xq28
Menkes syndrome	Growth deficiency, full cheeks, sparse kinky hair, metaphyseal changes, limited spontaneous movement, hypertonicity, seizures, hypothermia, lethargy, arterial tortuosity, death in early childhood	*ATP7A,* Xpl3.3
Pelizaeus–Merzbacher disease	Nystagmus, truncal hypotonia, progressive spastic paraplegia, ataxia, dystonia	*PLP,* Xq21.1
Renpenning syndrome (includes Sutherland–Haan, cerebropalatocardiac, Golabi–Ito–Hall, Porteous syndrome	Short stature, microcephaly, small testes. May have ocular or genital abnormalities	*PQBP1,* Xp11.3
Rett syndrome	XLMR in girls, cessation and regression of development in early childhood, truncal ataxia, autistic features, acquired microcephaly	*MECP2,* Xq28
X-linked hydrocephaly-MASA spectrum	Hydrocephalus, adducted thumbs, spastic paraplegia	*L1CAM,* Xq28

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practice" or mandatory and believed that decisions regarding "cranial imaging will need to follow (not precede) a thorough assessment of the patient and the clinical presentation." In contrast, van Karnebeek et al[12] found that MRI alone leads to an etiologic diagnosis in a much lower percentage of patients studied. They cited Kjos et al,[72] who reported diagnoses in 3.9% of patients who had no known cause for their ID and who did not manifest either a progressive or degenerative course in terms of their neurologic symptomatology. Bouhadiba et al[73] reported diagnoses in 0.9% of patients with neurologic symptoms, and in 4 additional studies, no etiologic or syndromic

diagnosis on the basis of neuroimaging alone was found.[65,69,74,75] The authors of 3 studies reported the results on unselected patients; Majnemer and Shevell[67] reported a diagnosis by this typed unselected investigation in 0.2%, Stromme[76] reported a diagnosis in 1.4% of patients, and van Karnebeek et al[40] reported a diagnosis in 2.2% of patients.

Although a considerable evolution has occurred over the past 2 decades in neuroimaging techniques and modalities, for the most part with the exception of proton magnetic resonance spectroscopy, this has not been applied or reported in the clinical situation of developmental delay/ID in childhood. Proton resonance spectroscopy provides a noninvasive mechanism of measuring brain metabolites, such as lactate, using technical modifications to MRI. Martin et al[77] did not detect any differences in brain metabolite concentrations among stratifications of GDD/ID into mild, moderate, and severe levels. Furthermore, they did not detect any significant differences in brain metabolite concentration between children with GDD/ID and age-matched typically developing control children. Thus, these authors concluded that proton resonance spectroscopy "has little information concerning cause of unexplained DD." Similarly, the studies by Martin et al[77] and Verbruggen et al[71] did not reveal that proton magnetic resonance spectroscopy was particularly useful in the determination of an underlying etiologic diagnosis in children with unexplained developmental delay/ID.

All of these findings suggest that abnormal findings on MRI are seen in ~30% of children with developmental delay/ID. However, only in a fraction of these children does MRI lead to an etiologic or syndromic diagnosis. The precise value of a negative MRI result in leading to a diagnosis has not yet been studied in detail. In addition, MRI in the young child with developmental delay/ID invariably requires sedation or, in some cases, anesthesia to immobilize the child to accomplish the imaging study. This need, however, is decreasing with faster acquisition times provided by more modern imaging technology. Although the risk of sedation or anesthesia is small, it still merits consideration within the decision calculus for practitioners and the child's family.[63,78,79] Thus, although MRI is often useful in the evaluation of the child with developmental delay/ID, at present, it cannot be definitively recommended as a mandatory study, and it certainly has higher diagnostic yields when concurrent neurologic indications exist derived from a careful physical examination of the child (ie, microcephaly, microcephaly, seizures, or focal motor findings).

RECOMMENDED APPROACH

The following is the recommended medical genetic diagnostic evaluation flow process for a new patient with GDD/ID. All patients with ID, irrespective of degree of disability, merit a comprehensive medical evaluation coordinated by the medical home in conjunction with the medical genetics specialist. What follows is the clinical genetics evaluation (Fig 1):

1. Complete medical history; 3-generation family history; and physical, dysmorphologic, and neurologic examinations.
2. If the specific diagnosis is certain, inform the family and the medical home, providing informational resources for both; set in place an explicit shared health care plan[80] with the medical home and family, including role definitions; provide sources of information and support to the family; provide genetic counseling services by a certified genetic counselor; and discuss treatment and prognosis. Confirm the clinical diagnosis with the appropriate genetic testing, as warranted by clinical circumstances.
3. If a specific diagnosis is suspected, arrange for the appropriate diagnostic studies to confirm including single-gene tests or chromosomal microarray test.
4. If diagnosis is unknown and no clinical diagnosis is strongly suspected, begin the stepwise evaluation process:
   a. Chromosomal microarray should be performed in all.
   b. Specific metabolic testing should be considered and should include serum total homocysteine, acyl-carnitine profile, amino acids; and urine organic acids, glycosaminoglycans, oligosaccharides, purines, pyrimidines, GAA/creatine metabolites.
   c. Fragile X genetic testing should be performed in all.
5. If no diagnosis is established:
   a. Male gender and family history suggestive X-linkage, complete XLID panel that contains genes causal of nonsyndromic XLID and complete high-density X-CMA. Consider X-inactivation skewing in the mother of the proband.
   b. Female gender: complete *MECP2* deletion, duplication, and sequencing study.
6. If microcephaly, macrocephaly, or abnormal findings on neurologic examination (focal motor findings, pyramidal signs, extrapyramidal signs, intractable epilepsy, or focal seizures), perform brain MRI.
7. If brain MRI findings are negative or normal, review status of diagnostic evaluation with family and medical home.
8. Consider referrals to other specialists, signs of inborn errors of metabolism

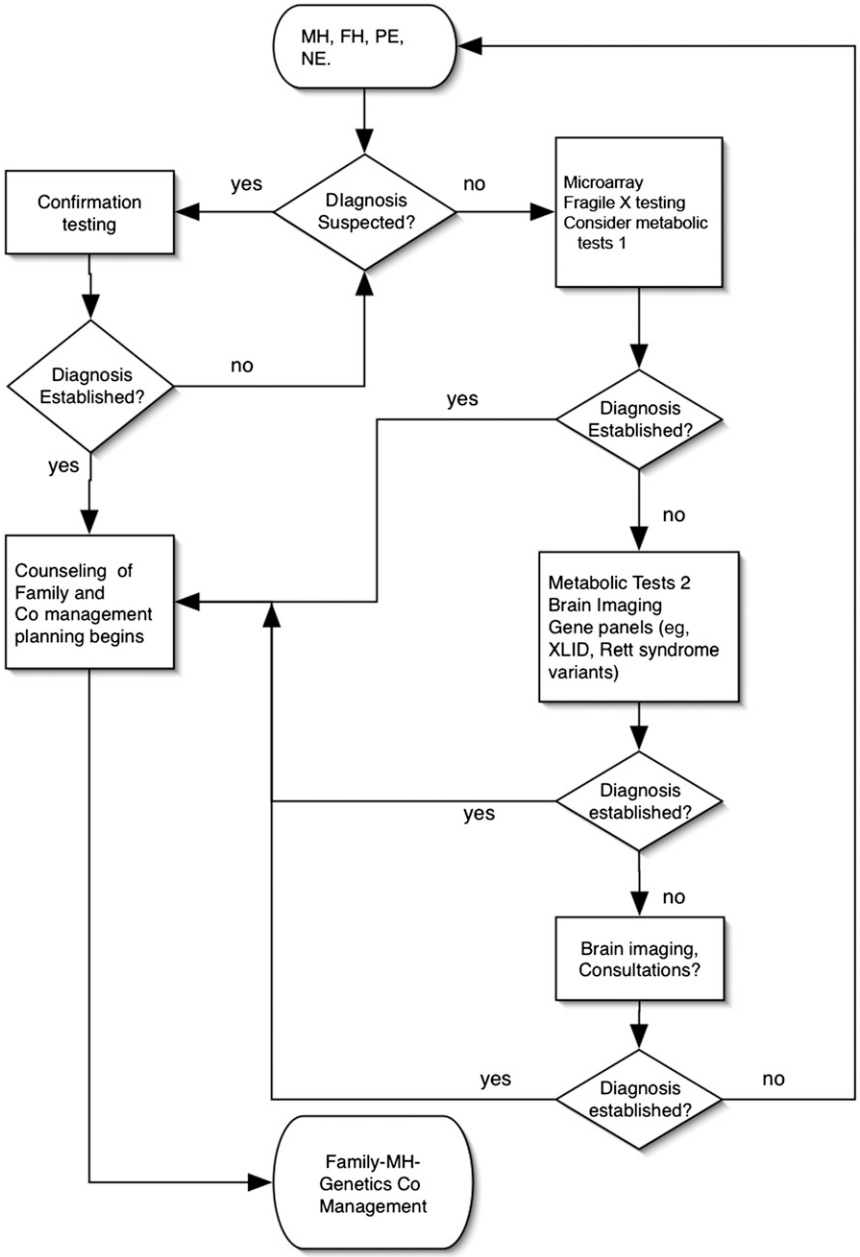

FIGURE 1

Diagnostic process and care planning. Metabolic test 1: blood homocysteine, acylcarnitine profile, amino acids; and, urine organic acids, glycosaminoglycans, oligosaccharides, purines, pyrimidines, GAA/creatine metabolites. Metabolic test 2 based on clinical signs and symptoms. FH, family history; MH, medical history; NE, neurologic examination; PE, physical and dysmorphology examination.

for which screening has not yet been performed, etc.

9. If no further studies appear warranted, develop a plan with the family and medical home for needed services for child and family; also develop a plan for diagnostic reevaluation.

THE SHARED EVALUATION AND CARE PLAN FOR LIMITED ACCESS

Health care systems, processes, and outcomes vary geographically, and not all of what is recommended in this clinical report is easily accessible in all regions of the United States.[21,81–84] Consequently, local factors affect the process of evaluation and care. These arrangements are largely by local custom or design. In some areas, there may be quick access and intimate coordination between the medical home and medical genetics specialist, but in other regions, access may be constrained by distance or by decreased capacity, making for long wait times for appointments. Some general pediatricians have the ability to interpret the results of genetic testing that they may order. In addition, children with GDD or ID are often referred by pediatricians to developmental pediatricians, child neurologists, or other subspecialists. It is appropriate for some elements of the medical genetic evaluation to be performed by physicians other than medical geneticists if they have the ability to interpret the test results and provide appropriate counseling to the families. In such circumstances, the diagnostic evaluation process can be designed to address local particularities. The medical home is responsible for referrals of the family and child to the appropriate special education or early developmental services professional for individualized services. In addition, the medical home can begin the process of the diagnostic evaluation if access is a problem and in coordination with colleagues in medical genetics.[80,85] What follows is a suggested process for the evaluation by the medical home and the medical genetics specialist and only applies where access is a problem; any such process is better established with local particularities in mind:

Medical home completes the medical evaluation, determines that GDD/ID is present, counsels family, refers to educational services, completes a 3-generation family history, and completes the physical examination and addresses the following questions:

1. Does the child have abnormalities on the dysmorphologic examination?

   a. If no or uncertain, obtain microarray, perform fragile X testing, and consider the metabolic testing listed previously. Confirm that newborn screening was completed and reported negative. Refer to medical genetics while testing is pending.
   b. If yes, send case summary and clinical photo to medical genetics center for review for syndrome identification. If diagnosis is suspected, arrange for expedited medical genetics referral and hold all testing listed above. Medical geneticist to arrange visit with genetic counselor for testing for suspected condition.
2. Does the child have microcephaly, macrocephaly, or abnormal neurologic examination (listed above)? If "yes," measure parental head circumferences and review the family history for affected and unaffected members. If normal head circumferences in both parents and negative family history, obtain brain MRI and refer to medical genetics.
3. Does child also have features of autism, cerebral palsy, epilepsy, or sensory disorders (deafness, blindness)? This protocol does not address these patients; manage and refer as per local circumstances.
4. As above are arranged and completed and negative, refer to medical genetics and hold on additional diagnostic testing until consultation completed. Continue with current medical home family support services and health care.
5. Should a diagnosis be established, the medical home, medical geneticist, and family might then agree to a care plan with explicit roles and responsibilities of all.
6. Should a diagnosis not be established by medical genetics consultation, the medical home, family, and medical geneticist can then agree on the frequency and timing of diagnostic reevaluation while providing the family and child services needed.

EMERGING TECHNOLOGIES

Several research reports have cited whole-exome sequencing and whole-genome sequencing in patients with known clinical syndromes for whom the causative gene was unknown. These research reports identified the causative genes in patients with rare syndromes (eg, Miller syndrome,[86] Charcot-Marie-Tooth disease,[87] and a child with severe inflammatory bowel disease[88]). Applying similar whole-genome sequencing of a family of 4 with 1 affected individual, Roach et al[86] identified the genes for Miller syndrome and primary ciliary dyskinesia. The ability to do whole-genome sequencing and interpretation at an acceptable price is on the horizon.[87,89] The use of exome or whole-genome sequencing challenges the field of medical genetics in ways not yet fully understood. When a child presents with ID and whole-genome sequencing is applied, one will identify mutations that are unrelated to the question being addressed, in this case "What is the cause of the child's intellectual disability?" One assumes that this will include mutations that families do not want to have (eg, adult-onset disorders for which no treatment now exists). This is a sea change for the field of medical genetics, and the implications of this new technology have not been fully explored. In addition, ethical issues regarding validity of new tests, uncertainty, and use of resources will need to be addressed as these technologies become available for clinical use.[90,91]

CONCLUSIONS

The medical genetic diagnostic evaluation of the child with GDD/ID is best accomplished in collaboration with the medical home and family by using this clinical report to guide the process. The manner in which the elements of this clinical protocol are applied is subject to local circumstances, as well as the decision-making by the involved pediatric primary care provider and family. The goals and the process of the diagnostic evaluation are unchanged: to improve the health and well-being of those with GDD/ID. It is important to emphasize the new role of the genomic microarray as a first-line test, as well as the renewal of efforts to identify the child with an inborn error of metabolism. The future use of whole-genome sequencing offers promise and challenges needing to be addressed before regular implementation in the clinic.

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