inborn error of metabolism, such as the maple syrup odor to urine or ear wax in maple syrup urine disease.[24]

Family History

Obtaining a 3-generation pedigree (asking specific questions about siblings, parents, grandparents, aunts, and uncles) provides important information. Additional family history of GDD/ID may suggest a specific mode of inheritance. Absence of other affected individuals may suggest autosomal recessive inheritance, a de novo autosomal dominant disorder, or an X-linked disorder. A history of psychiatric disorders and/or seizures is another potential indicator of genetic disorders in patients with GDD/ID, because some genetic disorders associated with GDD/ID can manifest with psychiatric symptoms and/or epilepsy in other family members as the result of incomplete penetrance and variable expressivity. In addition, psychiatric conditions can indicate genetic predisposition in their children. A family history of premature ovarian failure or ataxia/tremor may suggest fragile X syndrome.[25] A family history of 3 or more miscarriages in an individual may suggest a balanced chromosome rearrangement in a parent, predisposing to an unbalanced structural chromosome abnormality in offspring. Advanced paternal age may suggest a de novo dominant disorder, whereas advanced maternal age (>35 years) may suggest an aneuploidy. In vitro fertilization is associated with an increased risk of imprinting disorders, such as Prader-Willi syndrome and Angelman syndrome.[26,27]

Clinical Examination

Accurate assessment of height, weight, and head circumference is important, because these may inform the differential diagnosis. With respect to head circumference, analysis of growth velocity using a standardized growth curve will identify microcephaly (noting whether the microcephaly is congenital or postnatal), plateauing head circumference, and progressive microcephaly or macrocephaly. It is important to assess weight gain and growth to assess for failure to thrive.

Notation of dysmorphic features and other congenital anomalies, such as limb defects, will indicate the need for referral of the patient to a geneticist for further dysmorphology evaluation. For example, dysmorphic craniofacial features may include abnormal head shape, abnormally spaced or upslanting/downslanting eyes, epicanthal folds, depressed nasal bridge, unusual nasal configuration, long philtrum, and ear abnormalities.

Examination of the skin for neurocutaneous stigmata, such as café au lait macules, other hypo- or hyperpigmented skin regions, or vascular skin markings may indicate specific disorders. Rarely, hair or nail abnormalities also may suggest a specific disorder. A precordial examination may detect a murmur indicative of underlying congenital heart disease. Hepatosplenomegaly can be a feature of genetic overgrowth disorders and some inborn errors of metabolism (eg, lysosomal disorders). Cryptorchidism can be associated with some genetic neurodevelopmental disorders. Vision and hearing screening can also be performed by the pediatrician. A complete neurologic examination may detect abnormalities of muscle tone, weakness, or a movement disorder.

Corollary Testing: Neuroimaging, Vision, Hearing

In children with GDD/ID, evaluation by an ophthalmologist should be considered, both for diagnostic and therapeutic purposes. Retinal and optic nerve abnormalities may provide insight into an underlying genetic disorder. In children with language delay, hearing evaluation is also important. In addition to facilitating treatment, the finding of sensorineural hearing loss may offer a phenotypic clue.[28]

Neuroimaging with magnetic resonance imaging (MRI) is indicated in children with GDD/ID and abnormal head circumference, focal neurological signs or symptoms, seizures, increased tone or developmental regression.[5,29] It may also be considered in moderate to severe GDD/ID, if a specific disorder with abnormal neuroimaging is suspected, or if no etiology is identified following other diagnostic evaluations including genetic studies.[19] Neuroimaging may demonstrate relatively nonspecific findings, such as underrotated hippocampi, abnormally contoured and enlarged ventricles, reduced cerebral volume, delayed myelination, or dysgenesis of corpus callosum. It may also demonstrate more specific structural abnormalities, such as polymicrogyria, lissencephaly, periventricular nodular heterotopia, holoprosencephaly, or cerebellar malformations. There may also be signal abnormalities of the cerebral white matter or basal ganglia that can occasionally suggest a specific disorder based on the pattern.[30] Magnetic resonance spectroscopy may be useful in the evaluation for some inborn errors of metabolism, including disorders of creatine metabolism.[31]

AGNOSTIC APPROACH TO DIAGNOSTIC EVALUATION

If the medical history, family history, clinical examination, and corollary testing do not lead to a suspected diagnosis, then a hypothesis-free algorithmic approach could be pursued. This approach considers diagnostic yield, cost and complexity of the test, and the potential impact of the test results. Previously published agnostic approaches include a prior iteration from the American Academy of Pediatrics (AAP), and recommendations from the American Academy of Neurology (AAN), Canadian Pediatric Society (CPS), and the Treatable Intellectual Disability Endeavor (TIDE) protocol.[1,5,32] The AAP proposes the following updated tiered agnostic approach based on diagnostic yield and practical considerations (see Figure 1). Depending on comfort level, the pediatrician may opt to refer to a geneticist at any point in the genetic diagnostic evaluation. If a geneticist is not available, higher-order evaluation from neurologists