IWGGD The International Working Group on Gaucher Disease

Guideline	**Symptomatic care of children with non-neuronopathic Gaucher disease**.
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Overview	In general, the Gaucher-disease specific treatment of children (< 18 years) with Gaucher disease needs to follow the recommendations stated in the treatment and monitoring working group (WG). The aim of this report is to emphasize supportive management points important for the **symptomatic care of children with non-neuronopathic Gaucher disease**. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty in the evidence and formulate recommendations (https://www.gradeworkinggroup.org)(1)(1).
Sections	

Physical growth

Recommendation: The panel recommends routine height and weight assessment for children with GD to determine growth percentile and growth rate.

Remarks:

- Preferable using growth charts that are population specific.
- A decline in height percentiles during follow-up could be secondary to complications/manifestations of GD or a co-morbidity (such as Celiac, growth hormone deficiency, etc.)
- Child height should be compared to expected mid-parenteral height.
- When possible, consultation with an expert in pediatric endocrinology helps evaluate other causes for growth delays in relevant cases.

Details: Height and weight may be severely affected in children with GD (2). In cases of earlier onset of clinical signs and symptoms, children's height and weight may be low below the 3rd percentile for their age. Even in mildly affected children, approximately half of the children present with height and weight growth percentiles ≤ 25%. Timely initiation of GD-specific therapy is important in symptomatic children to achieve normal growth (3, 4). Enzyme replacement therapy (ERT) was shown to accelerate the growth rate in children with GD. The therapeutic goal of ERT is to normalize growth and reach the peak of bone acquisition within three years of treatment onset.

The abnormal growth rate in children with mild signs of GD or children receiving GD-specific therapy can occasionally result from non-GD causes like celiac disease, growth hormone deficiency, etc. Improvements in growth hormone deficiency in symptomatic children after ERT initiation suggest that the growth hormone deficiency may be related to the coexistence of hypermetabolism with healthy thyroid functioning (5).

Delayed puberty, which often occurs in children with GD, can impact final height. Due to a longer time of growth, asymptomatic/mildly affected children, specifically those homozygous for the N370S mutation and those diagnosed through screening, are expected to reach a normal final height in their adulthood (2, 6).

As a measure of developmental age, or physiological maturity, bone age can represent more truthfully than chronological age, i.e., how far an individual has progressed towards full maturity. In children with GD, bone age is often delayed allowing catch-up growth after initiation of ERT (5).

Development milestones

Recommendation: For children with GD, the panel recommends routine assessment of developmental milestones, including motor, mental, social, visual, and auditory milestones

Remarks:

- Developmental milestones of children with GD type 1 should be similar to the general population.
- In severely symptomatic cases, normal development, especially motor milestones, may be affected by severe anemia and/or enlarged abdominal organs.
- Improved disease manifestations with ERT initiation should help achieve normal development (3, 4).

Dental health

Recommendation: The panel recommends regular oral examinations with appropriate dental treatment for children with GD as for other individuals.

Remarks:

- Consultation between the dentist and physician, preferably one with GD experience, should be considered when invasive procedures are planned.

Details: Oral and dental manifestations are not commonly seen in children with GD. These manifestations are often asymptomatic, although routine dental x-rays may detect them. The presence of pseudo-cystic or honeycombed radiolucent lesions, mainly in the premolar-molar regions, were reported, while osteonecrosis of the jaw is more rarely described (7-9). Delayed permanent dentition was found to be associated with mild to moderate bone involvement in children. Dental pulps can be infiltrated with Gaucher cells in severe type 1 GD (10). Oral hygiene in patients with GD was not different from otherwise healthy cohorts (11). Thrombocytopenia, coagulopathy, and platelet dysfunction, described in patients with GD, can increase the risk of gingival bleeding and of dental procedure-related bleeding (12) [see below – bleeding tendency section, for more details].

Iron deficiency anemia (IDA)

Recommendation: The forum considers a good practice to diagnose and manage iron deficiency in children with GD

Remarks:

- GD-related hyperferritinemia, although not commonly encountered in the pediatric age group, may mask iron deficiency. In those cases, reduced iron, reduced transferrin saturation, increased total iron-binding capacity (TIBC), or increased soluble transferrin receptors can be used to indicate iron deficiency (13-15).
- Iron supplementation, e.g., 3-6 mg/kg/day, for three months monitored by iron profile, and treatment of the underlying cause, if applicable, is recommended, as per the general population.
- Nutritional Iron deficiency is considered the most common cause of anemia. Other reasons reported in children with GD, like recurrent epistaxis, menorrhagia, and celiac disease, should be investigated and treated.

Bleeding tendency

Recommendation: The panel recommends a full hematological assessment before invasive procedures or surgeries and in cases of increased bleeding tendency. We recommend performing a detailed history of bleeding tendency, history of hepatic involvement, complete blood count, coagulation tests, and specific coagulation factor assays if indicated and platelet function studies.

Remarks:

- Thrombocytopenia, coagulopathy, and platelet dysfunction seen in patients with GD increase the risk of bleeding, mainly mucocutaneous and procedure-related bleeding (16).
- Coagulation abnormalities usually resolve with ERT unless there is hepatic dysfunction, especially underlying cirrhosis in severe GD. Consistent abnormal coagulation tests should lead to further testing as suggested for non-GD patients (15)
- Platelet function defects may remain even after years of GD-specific therapy (16-18).

- In the case of suspected or proven bleeding tendency, expert hematology input is required.
- There is no GD-related contraindication for the use of antifibrinolytics, platelet and/or plasma transfusion in case of bleeding or in preparation for surgery, if needed.

Bone mineral density

Recommendation: The panel recognizes the need to understand better the use of bone mineral density testing in children with Gaucher disease

Remarks:

Childhood is a critical time for accrual of bone density, which peaks at 18-20 years of age. Both the infiltration of Gaucher cells to the bone and the inflammatory burden of GD may have a negative effect on bone density (19). Osteopenia is a relevant sign of bone involvement in Gaucher disease (GD) both in children and adults. Furthermore, abnormal bone metabolism is considered to play a role in the growth and pubertal delay.

The preferred skeletal sites for DXA measurements in children (usually after 10 years of age) are the lumbar spine (L1–L4) and total body-less head (20). In children with GD, like children with other chronic illnesses with delayed growth and pubertal development, the appropriate interpretation of DXA results requires adjusting the z score for height or height age and compared with reference data with age-, sex-, and height-specific z scores. Bone marrow density measured by DXA corrects bone mineral for the area (height and width) but not for the volume (height, width, and thickness) of bone. For this reason, if two individuals with identical "true" volumetric bone density are compared, the shorter person will have a lower BMD than the taller one. Similarly, a child with delayed puberty will not have had the same gains in bone size, geometry, and density. The Children's Hospital of Philadelphia online calculator based on the Zemel reference curves enables correction for height and height- z scores (https://zscore.research.chop.edu/bmdCalculator.php) (21).

The interpretation of bone densitometry results in children differs from that in older adults. The terms "osteopenia" and "osteoporosis" based on bone densitometry findings alone should not be used in younger patients; instead, bone mineral content or density that falls >2 SDs below expected is labeled "low for age." Pediatric osteoporosis is defined by using one of the following criteria: ≥1 vertebral fracture occurring in the absence of local disease or high-energy trauma (without or with densitometry measurements) or low bone density for age and a significant fracture history (defined

as ≥two long bone fractures before ten years of age or ≥three long bone fractures before 19 years of age) (13).

All strategies to optimize bone health should be considered. Timely initiation of ERT in children can help preserve BMD (22, 23). Calcium and vitamin D intake should be based on country or regional specific guidelines. Weight-bearing activity and short periods of high-intensity exercise (e.g., jumping 10 minutes/day, three times/week) should be encouraged. Reducing inflammation, undernutrition, or hormone imbalances also is necessary.

Routine pediatric health care

Recommendation: Where available, the panel suggests that children with GD will be followed by a pediatrician expert in GD on a routine basis, usually every 6-12 months (24, 25).

Remarks:

- Children with GD should continue their routine pediatric health care by a local health provider (usually a pediatrician), including the recommended vaccination program
- Nutritional advice should be proposed to the children's parents with the aim to keep a healthy diet.

Psychosocial/behavioral assessment

Recommendation: The panel suggests including psychosocial support team as part of the Gaucher clinic.

Points to consider:

Having GD can take a psychological toll on children, adolescents, and adults (26). Specific disease manifestations such as organomegaly, delayed puberty, and growth retardation may affect body image and self-esteem while eliciting feelings of insecurity and isolation, which can lead to the development of behavioral problems. Additionally, chronic pain and fatigue may interfere with normal socialization and school performance. Children with GD report significantly lower health-related quality of life across all domains relative to healthy counterparts (27).

A diagnosis of genetic disease challenges both the child and the parents. Questions like -

why me? Why my child? The parent may feel responsible since he/she is the carrier.

Social determinants, religious principles, cultural beliefs, and practices may influence the uptake of information and understanding of genetic disease (28).

Monitoring children with GD must include regular psychosocial, functional, and quality-of-life evaluation (24).Psychosocial evaluation can be arranged to assess patients in friendly GD group gatherings so making them feel they are part of a community allowing for a better and more informative assessment

Physical activity

Recommendation: The forum considers good practice for children with GD to participate in regular physical activity as recommended for age-matched peers.

Remarks:

- The risk of specific physical activities in children with massive splenomegaly, severe anemia, bleeding risk, and/or bone disease should be assessed on an individual basis and should be re-assessed upon response to ERT

Details: Physical activity is associated with many physiological and psychological health benefits across the lifespan. International guidelines suggest that children should be participating in a minimum of 60 min of moderate to vigorous-intensity physical activity per day to achieve these benefits (29). For patients with GD, maintaining regular physical activity is further important to maintain bone health and help prevent bone loss (19).

The risk of splenic rupture is considerably low; still, for children who have very enlarged spleens, contact sports like football and basketball probably should be avoided in favor of activities like swimming, bike riding and dance programs. The risk of bleeding secondary to sport actives should be evaluated regularly.

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