High energy expenditure in a patient with feeding problems and Noonan syndrome spectrum disorder

Dagmar Tiemens, Annemiek van Wegberg, Debbie van Druten, Jos Draaisma

SUMMARY
Feeding problems are present in more than 50% of patients with a Noonan syndrome spectrum disorder in the first years of life. Food intake problems like severe or frequently vomiting may not only affect growth and development, but may also influence the process of learning how to eat and can have a great impact on the whole family. In addition to food intake problems, there is growing evidence that patients with a Noonan syndrome spectrum disorder may have a lower body mass index (BMI) due to a high energy expenditure, although little is known about the actual energy intake patients with a Noonan syndrome spectrum disorder need to maintain a healthy BMI. This article illustrates the challenge to recognise a high energy expenditure especially when a patient frequently vomits. Multidisciplinary attention is needed to manage food intake, vomiting and energy expenditure problems in patients with a Noonan syndrome spectrum disorder.

BACKGROUND
Noonan syndrome spectrum disorders are a group of phenotypically related conditions, resembling Noonan syndrome, caused by germ-line pathogenic variants in genes within the Ras/mitogen-activated protein kinase (Ras/MAPK) signalling pathway. The most prevalent syndrome is Noonan syndrome (OMIM 163950). The clinical presentation is extremely variable. Other Noonan syndrome spectrum disorders are Noonan syndrome with multiple lentigines (OMIM 151100), Noonan syndrome with loose anagen hair (OMIM 607721), cardio-faciocutaneous syndrome (OMIM 115150) and Costello syndrome (OMIM 218040).1 Key features of these disorders are heart problems and short stature. Several aspects of energy homeostasis problems, like food intake problems, energy expenditure and subsequent effects on growth and development have received less attention. This article aims to illustrate the complexity of food intake difficulties, energy requirement and growth problems. It is important to increase insight into the frequency and origin of these problems among patients with a Noonan syndrome spectrum disorder to develop evidence based guidelines for both food intake and energy expenditure problems.

CASE PRESENTATION
General
The girl was born after 35+5 weeks gestation complicated by polyhydramnios, for which amnion fluid drainage was performed. Birth weight was 3.39 kg (SDS +1.96). In her first year the clinical diagnosis of Noonan syndrome with loose anagen hair was confirmed genetically due to a pathogenic SHOC2 variant.

After birth it took 14 days for the patient to be able to be bottle-fed. At the age of 8 weeks, the ability of bottle-feeding declined and she was admitted to the hospital. No apparent cause of the bottle refusal could be found. She was discharged a week later completely dependent on tube-feeding, administered with a syringe (bolus). Initially a bottle was offered before administering the infant formula by tube without any noticeable improvement in feeding behaviour.

At the age of 3 months, she developed vomiting problems with a frequency of 15 to 20 times a day.

A feeding pump was required. Lowering the pump speed to 200 mL/hour had no positive effects.

No anatomical abnormalities were observed by an upper gastrointestinal barium contrast study, pH-metry showed no definite acid gastrooesophageal reflux. No additional examinations were performed, as bowel movements and defecation patterns were normal. Treatment was started with daily dosages of domperidone without improvement. Ultimately, although the frequency of vomiting continued, the total amount of food intake improved by lowering the pump speed to 50 mL/hour, thereby reducing the volume of the vomit. To ensure an adequate intake, she was fed continuously from 07.00 to 23:00 hour. At the age of 1 year, she received a gastrostomy. After a period of 3 months, the treatment of domperidone was replaced by erythromycin without improvement. The frequency of vomiting did not change until the age of 2 years. Although weight issues remained a concern, testing the calorie intake requirement was not indicated because weight for length remained within the normal ranges (table 1).

After the age of 2 years the vomiting frequency lowered to once or twice daily, altered with periods with higher frequencies, mostly coinciding with nose, throat or ear infections. At the age of 3 years and 9 months however her length SDS decreased to −4.08 with a weight for height SDS of −1.0, which stayed more or less the same until the age of 5 years (table 1). At the age of 5 years and 2 weeks, growth hormone therapy...
started and her length increased significantly. The frequency of the vomiting increased again during a persisting middle ear infection. At the age of 5 years and 3 months the vomiting was successfully treated with ondansetron. To the family, this cure was an important medical milestone, because of the extended effects in terms of attention for the other children, mobility, socially and on providing the possibility for both parents to be able to work.

Several speech therapists have examined her feeding technique over the years. No relevant oral motor problems were found. The cause of the food refusal was established at the age of 6 years and 7 months using clinical psychological interview techniques, questionnaires and behavioural observations. The combination of various negative experiences in the mouth and throat area (the frequent vomiting, recurring ear and throat infections and the nasogastric tube) from a young age most likely have led to negative and physical associations with food. This prevented her from getting motivated to learn how to eat, did increase the fear for food and the consequences it might have, which led to a pattern of avoidance and food refusal behaviour. The patient was diagnosed with avoidant restrictive food intake disorder (ARFID).

Additional problems

Other physical problems of this patient besides haemodynamically not-important heart problems (atrial septal defect of the secundum type and stenosis of the left pulmonary artery) included chronic middle and outer ear, nose and skin infections (buttocks and eczema). These problems continued from the age of 3 months, with quieter periods in the summer and more issues in the winter periods. The itching causes scratching and an ongoing contamination from one site of infection to the next. The ear infections often coincided with a higher frequency of the vomiting.

INVESTIGATIONS

Detecting a high resting energy expenditure

During the food refusal therapy that started at the age of 6 years and 7 months calorie and fluid intake, amount and type of food were noted daily. Weight (weekly) and length (monthly) were measured. The patient started the treatment with high-calorie tube feeding, which was and remained over 120% of the recommended daily energy allowance (table 1).

During the eating therapy the transition from tube feeding to oral feeding was performed. Oral feeding diet was held initially at a daily intake of 96 kcal/kg instead of more than 120 kcal/kg/day in the 2 years before. By the time the patient turned 7 years old it was established that her weight did not increase enough with this amount of energy intake. So, at discharge, aged 7 years and 3 months the diet was increased to an intake of 100 kcal/kg per day.

After the eating therapy, following the high calorie diet, she used seven meals a day. Each meal took a considerable amount of time and instructions of the behavioural therapist of the treating specialised feeding clinic were given to all persons involved the care of the patient (nonprofessionals and professionals, for example, teachers, class and day care assistants). The body mass index (BMI) of the patient dropped considerably. From the age of 6.5 to 9 years her average BMI was less than −1.0 SDS, following the oral diet of approximately 90 kcal/kg/day (table 1).

As can be seen in table 1, she received an average intake of (far) more than 120% of the recommended daily allowance of energy in her life until now, without gaining sufficient weight in some periods. Additional investigation showed that the high energy requirement was not due to malabsorption. In February 2021 (age 12 years, 8 months) the resting energy expenditure (REE) was measured using an indirect calorimetry (Cosmed Quark RMR with canopy), after an overnight fast according to the Dutch national standard operating procedure. The measured REE was 1915 kcal/day with an respiratory quotient of 0.80, which is within normal ranges. The predictive equations of WHO and Schofield estimated an REE of respectively 1217 kcal/day and 1216 kcal/day. The actual REE was 1.57 higher than the estimated REE, thus confirming the high energy expenditure. Additional blood tests (iron status, vitamin B12 and folic acid) were normal. Bioelectrical impedance analysis (Inbody S10 device, Seoul, Korea) showed a decreased value for muscle tissue and an increased value for adipose tissue.

| Age in years | Length (cm) | Length in SDS | Weight (kg) | Weight (SDS) | BMI in SDS | Intake in kcal/kg/day | RDA in kcal/kg/day | Intake % of RDA |
|--------------|-------------|---------------|-------------|--------------|------------|----------------------|------------------|----------------|
| 0.75         | 67          | −1.36         | 7.25        | −1.48        | NA         | 131                  | 84               | 156*           |
| 1.25         | 75.5        | −1.16         | 9.36        | −1.05        | NA         | 128                  | 83               | 154*           |
| 2.67         | 80.5        | −3.20         | 10.8        | −2.50        | +0.30      | 111                  | 83               | 134*           |
| 3.75         | 86.5        | −4.08         | 11.3        | −3.52        | −0.28      | 106                  | 83               | 128*           |
| 4.0          | 87.5        | −4.20         | 12.0        | −3.70        | −0.20      | 125                  | 66               | 189*           |
| 5.75         | 101.5       | −3.15         | 15.5        | −2.46        | −0.07      | 136                  | 66               | 206            |
| 6.5          | 109         | −2.40         | 15.9        | −2.68†       | −1.67†     | 123                  | 66               | 186            |
| 7            | 111.5       | −2.15         | 17.4        | −2.50        | −1.00      | 96                   | 66               | 145            |
| 8.2          | 120.3       | −2.05         | 19.9        | −2.43        | −1.33      | 88                   | 66               | 133            |
| 9.2          | 128.7       | −1.66         | 26.1        | −0.99        | −0.14      | 90                   | 55               | 164            |
| 11.2         | 140.3       | −1.54         | 31.8        | −0.94        | −0.44      | 74                   | 55               | 135            |
| 12.5         | 148.6       | −1.47         | 36.6        | −1.03        | −0.18      | 67                   | 55               | 122            |

RDA according to the Dutch dietary daily reference intakes for the general population.

*Actual intake might be lower due to the high frequency of vomiting.

†Before this measure, she was ill during a short period.

BMI, body mass index; RDA, recommended daily allowance.

**Table 1 Characteristics of growth and energy intake during the first 13 consecutive years**
DIFFERENTIAL DIAGNOSIS

To unravel the complexity of intake problems, energy requirement and growth problems in this girl the following differential diagnosis was made:

► Intrinsic feature of Noonan syndrome spectrum disorder: Growth in children with Noonan syndrome is impaired right after birth and only partially associated with feeding problems. In addition, several specific Noonan syndrome spectrum disorder related factors, including the type of gene, seem to influence growth in the first year. This continues thereafter, especially in individuals with certain pathologic gene mutations (including SHOC2), and BMI scores are lowest in individuals with pathologic SHOC2 variants. The cause of short stature in NS is still not clear. Although growth hormone secretion is usually normal, growth hormone deficiency have been described. Partial growth hormone insensitivity is the current hypothesis for short stature in NS, for which many children have been treated with growth hormone.

► Gastro-oesophageal reflux disease: The diagnosis of gastro-oesophageal reflux disease is based primarily on clinical suspicion, which can be strengthened by additional diagnostic investigations. However, there is no single gold standard. An upper gastrointestinal barium contrast study can be used to evaluate anatomic conditions that might mimic or predispose to gastro-oesophageal reflux disease such as oesophageal narrowing, pyloric stenosis, malrotation and duodenal stenosis. Today, there is no sufficient evidence to use pH-metry for the diagnosis of gastro-oesophageal reflux disease. This may explain the normal findings in the presented patient.

Feeding problems in patients with a Noonan syndrome spectrum disorder is described in more than 50% of young children. The documented presumed or proven cause was most often gastro-oesophageal reflux disease (68%). Also Shah et al documented gastro-oesophageal reflux disease in more than 40% of children with feeding problems, as well as delayed gastric emptying. Delayed gastric emptying may exacerbate any tendency to gastro-oesophageal reflux disease. Shah et al postulated that the cause of the feeding problems is a delayed gastrointestinal motor development which may improve with age.

Zhong et al postulated a model in which the process of vomiting and nausea is described with various neuroanatomical sites, neurochemicals, receptors and their potential intracellular signalling cascades. The vomiting of the patient in this case study was exclusively treatable with ondansetron, a 5-Hydroxytryptamine 3 (5-HT3) receptor antagonist. Enterochromaffin (EC) cells of the gastrointestinal tract synthesise 95% of the body 5-HT and release 5-HT in response to mechanical or chemical stimulation. EC cell 5-HT has physiological effects on gut motility, secretion and visceral sensation. It signals through afferent vagal nerves that (together with splanchnic nerves) lead to the dorsal vagal complex and interacts with higher autonomic, cognitive and emotional centres along with brainstem vestibular nuclei and the vestibular apparatus in the inner ear before motor output is generated via efferent vagal nerves leading to vomiting/emesis.

Although the underlying mechanism of the vomiting in these patients still remains unelucidated, animal model studies on nausea and vomiting postulate that emesis is induced through a 5-HT3 receptor calcium dependent pathway in which the Ras/MAPK signalling may play a regulating role. As a Noonan syndrome spectrum disorder is caused by Ras/MAPK hyperactivation, this may, additional to delayed gastric emptying and gastro-oesophageal reflux disease, in part, help to explain the vomiting in this patient.

► ARFID: food refusal problems may be caused by as well somatic as non-somatic factors. The definite cause of food refusal is often difficult to establish, and most often multifactorial.

► (High) REE: the REE can be measured by indirect calorimetry and is dependent on age, gender, fat-free mass, underlying disease and medication.

► Additional problems: also recurrent (upper airway) infections and cardiac disease can contribute to impaired growth and weight.

The working diagnosis of ARFID and high energy expenditure will be substantiated more in detail in the treatment section and discussion.

TREATMENT, OUTCOME AND FOLLOW-UP

Avoidant/restrictive food intake disorder

The food refusal problems were treated initially with two behavioural therapy sessions per half-day, twice a week at the age of 2 to 4 years without noticeable effect. At the age of 4, while attending healthcare specialised primary school, it was decided eating therapy was no longer indicated by the lack of success. In later years a subsequent treatment of her food refusal problems by a speech therapist continued with a frequency of two times a week with no significant results.

At the age of 6 years and 7 months the patient was included in a treatment programme at a clinic specialised in the treatment of severe feeding problems (ARFID). A multidisciplinary validated approach was used, based on (cognitive) behaviour therapy and the principles of applied behaviour analysis. Important features of this treatment are the rewarding of all behaviour appropriate to oral (food)acceptance and extinguishing long existed avoidance behaviour.

Therapy sessions were performed four times a day, 5 days a week. Sessions lasted for 20 min and started at a point in the eating process where the behavioural effects of the psychological trauma were not noticeable anymore. This meant accepting a drip of water applied by the index finger of the therapist at her mouth. In protocollled subsequent steps the patient learnt to accept a variety of liquid foods with spoon feeding. Oral intake increased and tube feeding could be reduced where the caloric intake had to remain the same. After 5 months of therapy, tube feeding at home in the evening after therapy sessions was no longer indicated. It was decided to extend the therapy to aim at eating a normal solid food diet.

After 7 months of eating therapy, the patient was capable to have an oral intake of a high calorie solid based diet. Tempo and technique of eating remained a concern. Chewy food like bread crusts remained time consuming. Also she was not able to transport food from outside the mouth onto the tongue, but instead she put the tongue against the palate and transported the food from under the tongue into her right cheek, chewing only at the right side of her mouth.

Growth problems

There was shown a decreased secretion of growth hormone. Growth hormone treatment had striking results. Growth hormone, started at the age of 5 years by a length of SDS
Case report

Patient’s perspective

In general
To our family, initially the impact of the diagnose of NS LAH was not a real big concern. The heart problems of our daughter were mild and the clinical diagnose of the clinical genetic Noonan Syndrome specialist indicated that our daughter would develop the mild variant of the syndrome.

Over the years, however, we would realise the extent of the disorder.

Her cognitive development stayed behind, in time she needed a specialist teaching programme for children with learning disabilities. To us, that came as a surprise, because she was supposed to have the mild variant of the syndrome.

Vomiting problems
The impact of the vomiting on our life turned out to be enormous. The vomiting first of all was a health concern. Did our daughter get enough food? What harm did the frequent vomiting do? Why did she refuse to eat? Especially the need of continuous pump feeding from 7.00 AM – 11.00 PM was a challenge. We had to carry both her and the pump everywhere we went. She needed changing a lot, both her clothes (because of the vomiting) and her diapers (7–8 times per day). Which meant that for a short period of time the pump needed to be disconnected. This delayed the hour that we could stop the pump in the evening and go to bed.

It also restricted us in our mobility: bringing the other children to school, going for groceries, visiting friends and family. It had impact on the attention we could give to our other children, the amount of laundry, cleaning in the house hold, on our social life’s and on our professional life’s.

On some occasions the care was so intense that a short period of hospitalisation was necessary.

Although after 2 years the frequency of vomiting declined significantly, the vomiting problem was not solved until our daughter received the proper medication at the age of 5.

Food refusal problems
Unfortunately, despite all positive effects of the ondansetron, it did not help our daughter with her food refusal behaviour. She stayed dependent on tube feeding with a feeding pump completely. We were told that the frequency of her eating therapy (two mornings a week, 2 sessions per time) would be sufficient for her to learn how to eat. We followed this advice for almost 5 years, while there was no apparent progress in her ability of eating. The problem was, there was hardly any alternative. Having her follow the intense daily therapy at a specialised clinic for the treatment of severe eating problems at that time, would mean having her hospitalised during the week at the other part of the country. Unfortunately that was no option.

By the time our daughter was 6 years old, we moved to the middle of the country. One of the consequences was, that eating therapy at a dependence of this clinic would be close by. So she could sleep at home. At the age of 6,5 eating therapy started.

The clinic established that the ongoing negative physical sensation in the area of the mouth, throat and ears, both as a result of the continuous vomiting and the recurring ear infections, had led to a psychological trauma. This stimulated long lasting avoidance behaviour and prevented her from getting motivated to learn how to eat. Additionally we want to pinpoint out that the food refusal was not initiated by the vomiting, as the vomiting developed a couple of weeks after our daughter refused to drink her bottle. We were told that after 2 months the initial reflexes of sucking extinguish and the somatic nerve system normally would take over, but for some reason, our daughter was not capable of doing so.

The clinic not only discovered the cause of her continuing food refusal behaviour, but taught her how to eat liquid food in half a year and solid food in the following 3 months. We were very happy with these results.

Detecting a high energy expenditure
In the years before the transition to eat independently, the amount of tube feeding she got was a lot more than was being subscribed. With all good intentions in helping us and comforting us, 5–6 separate diet specialists, general practitioners and paediatrics reassured us that our daughter really got more than enough food to grow and we did not have to worry about her development. But we continued having concerns about her need for food. We were the ones realising every day how much food she got, while staying very skinny. The moment she got a cold or got sick, she could lose 1 to 2 kg of her body weight in just a few days. There were no energy reserves in her body.

The clinic not only taught our daughter very successfully to eat, but also discovered that her body needed a lot more food than what is standard considered to be sufficient.

Later, these findings were confirmed by an indirect calorie metric measurement at the Radboudumc.

To us, it was a relief to finally got the objective proof of our suspicion of her high rate of metabolism. With the current mindset on healthy food (“go easy on macronutrients”) both in formal and informal care, it sometimes is a challenge to have others involved in her care known, that in the case of our daughter an apparent excess of macronutrients, is necessary to maintain her health with her specific body.

Because we no longer could see the exact amount of food intake she got like we did preparing the food for the feeding pump, and because we were so happy that our daughter was finally able to eat her meals all by herself, unfortunately, it took 2 years to realise that the high calorie diet that the clinic subscribed was still not enough to meet the high energy demands of her body.

As a positive consequence of the hospitalisation for her appendicitis in 2017, it became obvious to what extent she could lose weight while being sick. It was then decided to prescribe daily medical dietary supplements. To us, this decision was very important. Initially, to a little extent, we felt the medical food as a step backwards. But very soon we noticed that those extra daily calories really relieved the pressure induced by the seven high caloric and time consuming eating sessions per day and how well it helped her regaining and maintaining a more healthy weight up on to this date.

Future
We hope that this article in some way may contribute to the awareness of professionals what impact both vomiting and a high energy expenditure can have on a child with a Noonan Syndrome Spectrum Disorder (NSSD). Hopefully this may lead to an extent of possible treatments of vomiting problems. Especially in children with an NSSD, finding a proper treatment for vomiting may be the more important as these children additionally may have a higher demand for energy to maintain a healthy BMI and body composition. Also we hope that more research can be developed to learn about the causes of a high
Energy expenditure among NSSD children. Finally, we hope to contribute to an evaluation of the current clinical management guidelines on feeding problems. E.g., by adding ondansetron to this list of vomiting treatment and lowering the threshold for supplementary medical food. This may help improve the care of NSSD children.

Learning points

- It is important to consider if a high caloric diet is indicated in patients with NS spectrum disorder. Indirect caloric measurements can be considered to establish the resting energy expenditure.
- Vomiting problems can cause psychological traumatising effects on the ability of a child to learn how to eat, leading to persistent food refusal behaviour. Also, continuous vomiting contributes to risks of malnutrition on development and growth especially if the patient has a high energy expenditure. Additionally, the impact on the family of both the vomiting and the food refusal should be taken into consideration. For these reasons it is important to treat the vomiting problems and the food refusal problems at an early age the most efficient way. In this case ondansetron specifically provided for a very successful treatment.
- It is important to treat additional problems, especially those who seem to enhance the vomiting problems. In this case an ear surgery decreased the amount of ear infections significantly.
- Vomiting in a patient with NS spectrum disorder may be treatable by ondansetron, a 5-HT3 receptor antagonist.
- The combination of various negative experiences in the mouth and throat area from a young age most likely has led to negative and physical associations with food. This has led to a pattern of avoidance and food refusal behaviour, which was diagnosed as avoidant restrictive food intake disorder (ARFID). This is the first case with an NS spectrum disorder with ARFID in the biomedical literature.

-4.36, resulted in a recent length of SDS -1.47, a difference of 2.89 SDS.

Additional problems

Although persisting middle ear infections coincided with an incline of the reflux problems, these could successfully be treated with an appropriate dosage of ondansetron. Ear surgery lowered the frequency of ear infections significantly.

DISCUSSION

Food intake problems in relation to a high energy expenditure

Although assessment of feeding problems are included in the international Clinical Management Guidelines of NS, feeding problems are not mentioned in the diagnostic criteria of NS. There is growing evidence for the importance of several aspects of gaining and maintaining a healthy BMI in patients with a Noonan syndrome spectrum disorder. Over 50% percent of children with a Noonan syndrome spectrum disorder suffer from feeding problems. There is a need for a structural multidisciplinary intervention strategy, which is not yet incorporated in existing guidelines. Additionally, it is possible that a need for more energy intake is being masked by the feeding problems. Both energy supply and energy demand (metabolism, energy expenditure and storing energy in muscle, adipose and bone tissue) participate in the regulation of energy homeostasis. It is important to evaluate all aspects involved in not only length growth but also in maintaining a healthy weight (BMI) and body composition. Recently, it was shown that patients with an NS spectrum disorder in general show a decrease in BMI, with the greatest decrease seen in patients with a pathologic SHOC2 or KRAS variants. The patients in this study revealed more noticeable effects on declined muscle tissue than adipose tissue, as was the case in our patient. Malagutti et al showed a lower BMI in patients from 7 to 17 years with NS spectrum disorders. They wondered if pathologic gene variants associated with NS spectrum disorders could influence metabolism and control of energy storage, as two important hormones involved in insatiety signals (insulin and leptin) act also through the RAS/MAPK pathway. A study in patients with CS displayed an increased REE and a high calorie intake compared with the general dietary energy recommendations. So, food intake problems may be the more important because of growing evidence that a pathogen mutation in a component of the Ras/MAPK signalling pathway could play a role in an increased energy expenditure, an altered energy storage, altered constitution of muscle and adipose tissue and a reduced BMI.

Although all these studies show an impact of an NS spectrum disorder on the BMI and body composition, still little is known on the exact amount of food or energy intake these patients require to maintain a healthy BMI.

The BMI drop of the Noonan syndrome with loose anagen hair patient in this case report, despite the already high energy intake, is in line with all these findings and shows that at least this patient indeed needs a significantly higher energy intake than currently is thought to be sufficient to maintain a healthy BMI.

Therefore it is important to establish exactly if and to what extent other patients with a Noonan syndrome spectrum disorder, especially infants, require a higher calorie-intake to remain a healthy BMI, compared with the general population. This may lead to evaluate the food and calorie intake standards for patients with a Noonan syndrome spectrum disorder, for example, in the international Clinical Management Guidelines and might justify lowering the threshold for subscribing supplementary medical food.

Acknowledgements Jos Draisma is member of the European Reference Network for Developmental Anomalies and Intellectual Disability (ERN-ITHACA).

Contributors DT (author and mother of the child): conceptualisation and design of the article, data analysis and interpretation, drafting of the manuscript, approval of the final manuscript. AW: conceptualisation and design of the article, drafting of the manuscript, approval of the final manuscript. DvD: conceptualisation and design of the article, critical review of the manuscript, approval of the final manuscript. ID: conceptualisation and design of the article, data analysis and interpretation, critical review of the manuscript, approval of the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Consent obtained from parent(s)/guardian(s)

Provenance and peer review Not commissioned; externally peer reviewed.
Case report

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

ORCID ID
Jos Draaisma http://orcid.org/0000-0003-4829-6173

REFERENCES
1. Grant AR, Cushman BJ, Cavé H, et al. Assessing the gene-disease association of 19 genes with the RASopathies using the ClinGen gene curation framework. Hum Mutat 2018;39:1485–83.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). American Psychiatric Pub, 2013.
3. Croonen EA, Draaisma JMT, van der Burgt I, et al. First-year growth in children with Noonan syndrome: associated with feeding problems? Am J Med Genet A 2018;176:951–8.
4. da Silva FM, Jorge AA, Malaquias A, et al. Nutritional aspects of Noonan syndrome and Noonan-related disorders. Am J Med Genet A 2016;170:1525–31.
5. Malaquias AC, Jorge AAL. Activation of the MAPK pathway (RASopathies) and partial growth hormone insensitivity. Mol Cell Endocrinol 2021;519:111040.
6. Rosen R, Vandenplas Y, Singendonk M, et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for pediatric gastroenterology, hepatology, and nutrition. J Pediatr Gastroenterol Nutr 2018;66:516–54.
7. Draaisma JMT, Drossaers J, van den Engel-Hoek L, et al. Young children with Noonan syndrome: evaluation of feeding problems. Eur J Pediatr 2020;179:1683–8.
8. Shah N, Rodriguez M, Louis DS, et al. Feeding difficulties and growth retardation in Noonan's syndrome. Arch Dis Child 1999;81:28–31.
9. Zhong W, Shahbaz G, Teskey G, et al. Mechanisms of nausea and vomiting: current knowledge and recent advances in intracellular emetic signaling systems. Int J Mol Sci 2021;22:5797.
10. Zhong W, Chebolu S, Darmani NA. Thapsigargin-induced activation of Ca²⁺/CaMKII-ERK in brainstem contributes to substance P release and induction of emesis in the least shrew. Neuropharmacology 2016;103:195–210.
11. Bryant-Waugh R. Avoidant/restrictive food intake disorder. Child Adolesc Psychiatr Clin N Am 2019;28:557–65.
12. Romano AA, Allanson JE, Dahlgren J, et al. Noonan syndrome: clinical features, diagnosis, and management guidelines. Pediatrics 2010;126:746–59.
13. Dard L, Bellance N, Lacombe D, et al. Ras signalling in energy metabolism and rare human diseases. Biochim Biophys Acta Bioenerg 2018;1859:845–67.
14. Noronha RM, Villares SMA, Torres N, et al. Noonan syndrome patients beyond the obvious phenotype: a potential unfavorable metabolic profile. Am J Med Genet A 2021;185:774–80.
15. Tajan M, Paccoud R, Branka S, et al. The RASopathy family: consequences of germline activation of the Ras/MAPK pathway. Endocr Rev 2018;39:676–700.
16. Javed F, He Q, Davidson LE, et al. Brain and high metabolic rate organ mass: contributions to resting energy expenditure beyond fat-free mass. Am J Clin Nutr 2010;91:907–12.
17. da Silva FM, Jorge AA, Malaquias A, et al. Nutritional aspects of Noonan syndrome and Noonan-related disorders. Am J Med Genet A 2016;170:1525–31.
18. Malaquias AC, Brasil AS, Pereira AC, et al. Growth standards of patients with Noonan and Noonan-like syndromes with mutations in the RAS/MAPK pathway. Am J Med Genet A 2012;158A:2700–6.
19. Leoni C, Onisimo R, Giorgio V, et al. Understanding growth failure in Costello syndrome: increased resting energy expenditure. J Pediatr 2016;170:322–4.

Copyright 2022 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit https://www.bmj.com/company/products-services/rights-and-licensing/permissions/
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:
► Submit as many cases as you like
► Enjoy fast sympathetic peer review and rapid publication of accepted articles
► Access all the published articles
► Re-use any of the published material for personal use and teaching without further permission

Customer Service
If you have any further queries about your subscription, please contact our customer services team on +44 (0) 207111 1105 or via email at support@bmj.com.
Visit casereports.bmj.com for more articles like this and to become a Fellow.