Commentary

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Rare disorders: the role of accurate case-based research, inquiries and qualitative research

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Rare disorders have a prevalence of less than 1 in 100,000 to 200,000 individuals. Since it is assumed that more than 5,000 distinct rare diseases have been described today, rare conditions likely affect 4 to 6 percent of the population in total [1, 2]. The low number of individuals affected by a specific rare disease causes a number of problems. Firstly, there are sometimes substantial deficits in diagnostics and therapy. Secondly, adequate care is not feasible if a diagnosis is made late or is not made at all. Thirdly, only few centers can provide this care. Finally, a useful treatment is often not available and can only be developed when the mechanisms underlying the disease are understood [1, 2]. Hypokalemic salt-losing tubulopathies, such as Bartter and Gitelman syndromes, are a group of rare renal diseases, first described in 1962, which are transmitted as autosomal recessive traits [3, 4]. Bartter-Gitelman patients share several characteristics including hypokalemia (often with concurrent hypomagnesemia), alkalosis, normal or low blood pressure and activated renin-angiotensin-aldosterone and prostaglandin–kinin systems [3, 4]. Networking among different working groups identified the underlying loss of function mutations in various genes [3, 4]. Since 1998 our laboratory of medical genetics at the Policlinico of Milan, Italy, made the molecular diagnosis of either Bartter or Gitelman syndrome in more than 250 patients. Sophisticated design based research, clinical trials conducted in academic settings and molecular biology investigations are currently considered the gold standard throughout the world. However, research in rare and very rare diseases faces methodologic limitations by virtue of the very small number of participants available to be studied. In our experience, the management of patients affected with rare diseases greatly benefits from both case-based research and qualitative research.

Twenty-five years ago, we were deeply impressed by the case of a mentally retarded child with an unclassified variant of Bartter-Gitelman syndrome, who suddenly and unexpectedly died [5]. Since potassium depletion imparts a risk for cardiac arrhythmias, we tentatively attributed the death of the child to the dyselectrolytemia [6]. Unfortunately, we were not able to convincingly demonstrate that in Bartter-Gitelman patients the risk for developing hazardous cardiac arrhythmias is increased neither by assessing the QT interval on standard electrocardiography nor by monitoring continuous ambulatory electrocardiography and exercise testing [7, 8]. Considering the persisting uncertainty related to the possible occurrence of cardiac arrhythmias culminating in syncope or sudden death in the context of Bartter-Gitelman patients, we performed a systematic inquiry among physicians caring for children affected with these diseases. The inquiry disclosed four patients with lethal and three with almost lethal cardiac arrhythmias [9]. Without any doubt, it is currently accepted that, in Bartter-Gitelman patients, severe hypokalemia (2.0 mmol/L or less) may be responsible for life-threatening arrhythmias and sudden death [10]. The story of cardiac arrhythmias in Bartter-Gitelman patients illustrates problems that arise in the attempt to demonstrate uncommon complications in rare diseases. We were able to rapidly find the proverbial needle in the haystack ("acum in meta faeni quaerere") by means of a simple and cost effective inquiry among pediatric kidney disease specialists [9]. On the contrary, more sophisticated studies were not helpful [7, 8], suggesting that in the context of rare diseases inquiries among specialists may sometimes be an ingenious, straightforward and cheap strategy of research.

Figure 1 The proverbial needle in a haystack.

Gitelman disease is the most frequent variant of Bartter-Gitelman syndrome with a prevalence of carriers of approximately one percent in the general population. This tubulopathy is often considered, especially in childhood, a very benign condition, which is oligo- or asymptomatic [3, 4]. However, we and other authors were impressed by the fact that many adult patients report symptoms such musculoskeletal complaints, fatigue, dizziness, nocturia, polydipsia, polyuria, paresthesias or palpitations and a reduced general well-being [11]. On the other side, no study was so far able to establish a correlation between symptoms and biochemical values. These observations demonstrate that factors other than dyselectrolytemia modulate the experience of the disease in everyday life. We undertook a qualitative study [12] in Italian-speaking young adults affected with Gitelman disease. Fort this purpose we conducted in-dept interviews that were audio-recorded, transcribed and analyzed using the constant comparative method [12]. We found that Gitelman patients develop different interpretations of their symptoms, and that specific management behaviors and psycho-social risks are tied to each kind of interpretation [13]. Some affected patients consider Gitelman syndrome a “disabling illness”, some a “normalized illness”, some a “different normality” and some an “episodic disability” [13]. Based on the mentioned representation, patients develop peculiar ways of managing the condition in everyday life, forms of relationship with their doctor, lifestyles, and risks [13]. These data indicate that adult Gitelman patients have a wide margin of interpretation of their health condition, develop different interpretations of their symptoms, and that specific management behaviors and psychosocial risks are tied to each kind of interpretation. These findings could be used by physicians to adapt health care and information.

It is virtually impossible to improve the management for patients affected with rare diseases using conventional research strategies. The difficulties are due in part to the nature of rare diseases. The frequency of many of the disorders is so low that it is next to impossible in the short term to gather enough patients to achieve sufficient statistical power to demonstrate significant clinical benefits of a therapy. Moreover, the diseases are often complex and multisystem, and they tend to pursue highly variable clinical courses [1, 2]. Our experience documents that the management of these patients greatly benefits from accurate case-based research, from inquiries among clinical experts, qualitative research.

References

1 Iribarne A (2003) Orphan diseases and adoptive diseases. JAMA 290: 116

2 Rawlins MD (2005) Neglected diseases. BMJ 330: 376-377

3 Bettinelli A, Vezzoli G, Colussi G, Bianchetti MG, Sereni F, et al. (1998) Genotype-phenotype correlations in normotensive patients with primary renal tubular hypokalemic metabolic alkalosis. J Nephrol 11: 61-69

4 Seyberth HW, Schlingmann KP (2011) Bartter- and Gitelman-like syndromes: salt-losing tubulopathies with loop or DCT defects. Pediatr Nephrol 26: 1789-1802

5 Zanolari Calderari M, Vigier RO, Bettinelli A, Bianchetti MG (2002) Electrocardiographic QT prolongation and sudden death in renal hypokalemic alkalosis. Nephron 91: 762-763

6 Greenlee M, Wingo CS, McDonough AA, Youn JH, Kone BC (2009) Narrative review: evolving concepts in potassium homeostasis and hypokalemia. Ann Intern Med 150: 619-625

7 Bettinelli A, Tosetto C, Colussi G, Tommasini G, Edefonti A, et al. (2002) Electrocardiogram with prolonged QT interval in Gitelman disease. Kidney Int 62: 580-584.

8 Foglia PE, Bettinelli A, Tosetto C, Cortesi C, Crosazzo L, et al. (2004) Cardiac work up in primary renal hypokalaemia-hypomagnesaemia (Gitelman syndrome). Nephrol Dial Transplant 19: 1398-1402.

9 Cortesi C, Bettinelli A, Emma F, Fischbach M, Bertolani P, Bianchetti MG (2005) Severe syncope and sudden death in children with inborn salt-losing hypokalemic tubulopathies. Nephrol Dial Transplant 20: 1981-1983.

10 Cortesi C, Lava SAG, Bettinelli A, Tammaro F, Giannini O, et al. (2010) Cardiac arrhythmias and rhabdomyolysis in Bartter-Gitelman patients. Pediatr Nephrol 25: 2005-2008.

11 Cruz DN, Shaer AJ, Bia MJ, Lifton RP, Simon DB (2001) Gitelman's syndrome revisited: an evaluation of symptoms and health-related quality of life. Kidney Int 59: 710-717.

12 Mays N, Pope C (2000) Qualitative research in health care. Assessing quality in qualitative research. BMJ 320: 50-52.

13 Caiata-Zufferey M, Zanini CA, Schulz PJ, Syrén ML, Bianchetti MG, et al. (2012) Living with Gitelman disease: an insight into patients' daily experiences. Nephrol Dial Transplant 27: 3196-3201