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Paediatric care of the child with haemophilia

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Summary. The paediatric care of children with haemophilia in developed countries should focus on the health of the child, not on the disorder. Gene therapy offers the hope of an ultimate ‘cure’ for the disorder, but until this is a viable proposition, patients should be given more control over their treatment, and the focus should be on ‘self-monitored and self-adjusted’ prophylaxis. New instru-

ments for measuring joint function and radiographic changes, and quality of life are valuable tools in improving the treatment of paediatric care for children with haemophilia.

Keywords: haemophilia A, haemophilia B, factor VIII, factor IX.

Introduction

The future for a boy with newly diagnosed haemophilia is totally different in a developed compared with a developing country. As I work with children in Sweden, my perspective in this presentation is the perspective of a paediatrician in a developed country. What is today’s reality in some countries is the vision for tomorrow for other countries. The aim of my presentation is to focus on a few aspects of the care of the child with haemophilia which I think are important today, but also to take the opportunity to speculate or have visions for the future. The aim is not to give a comprehensive overview of all aspects of haemophilia care in children.

To focus on the healthy part of a child

In countries with limited resources for health care, it is natural that focus has to be on the disease itself, and literally how to survive from day to day. In most countries with well-developed health care, the ability to treat haemophilia has dramatically improved during the past decades due to the availability of factor VIII and factor IX concentrates. The focus in these countries should be switched towards the

healthy child and not the disorder itself. The word haemophilia and the description of the disorder have a great impact on how it is perceived by parents. It is a disease with a dramatic history; older persons with haemophilia and healthcare personnel remember how it once was in developed countries.

I think that the first information given to a family with a child who has been diagnosed as having haemophilia is of crucial importance and influences how this family and later the child will cope with haemophilia in their daily lives. For the family, the life with a child with haemophilia starts with this information and it is often given by a paediatrician. The experienced paediatrician knows how to inform parents that their child has a chronic disorder. The information should ideally be given to both parents and, if possible, together with older siblings. As we all know, parents are in a state of shock during this first talk and may only remember fragments of the information given. Our goal with this first talk should be that they understand that ‘it is possible to live a practically normal life with a normal life expectancy although you have haemophilia’. Usually the boy with haemophilia is too young to understand the information, but if he is a little older, one has to understand that the boy in this situation is in need of different information from parents. It is important that the boy does not feel guilt, having caused problems and sorrow to his parents for not being healthy. He has to understand that the sadness and sorrow the parents may show are signs of love for him. The small boy lives here and now and the future is only what will happen during the next hours or

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days – will the nurse take another blood sample? Does he have to stay in the hospital? These questions must be answered. The parents, however, have a totally different perspective of time in this situation, influenced by existential thoughts, for example, will he survive into adulthood? Will he be able to play as normal children? Will he be able to attend school and get an education? Parents usually feel guilt for the child being ill. It is easier to cope with something if there is an explanation to it. The mother who might be a genetic carrier is obviously at risk for feeling guilt for the child's disease but sometimes it may be totally irrelevant events in the past that are brought up as potential causes of the disorder. For an optimal outcome of the crisis reaction, it is important to try to find out if the parents have anything that they consider they have done wrong in the past as an explanation of the disorder.

The information given in the first conversation should be repeated in subsequent meetings with the parents to ensure that they have received all relevant information. Positive information such as treatment strategies with prophylaxis and the possibility to cure the disease in the near future by gene therapy should be given together with straightforward information about complications such as the development of inhibitors. All information during this sensitive period has to be communicated by the same doctor and nurse to avoid uncertainty and frustration, which could result from the slight interpersonal differences that exist between care-providers giving the same medical information. One may wonder why I put such effort into discussing these trivial things. It is my belief that the psychological events and processes at the time of diagnosis are the most important factors in deciding if later we have to deal with a 'haemophilic child in a haemophilia family' or 'a healthy family with a child who feels healthy, despite having a disorder called haemophilia'.

Gene therapy vs. prophylactic treatment

For the child with haemophilia, gene therapy is of course the ultimate goal. Today, primary prophylactic therapy may be considered as the gold standard of therapy. However, this therapy is only offered to a small proportion of children with haemophilia and, due to its cost, it is widely debated. We do not know when gene therapy will be a treatment option for all children with haemophilia and we do not know if it will offer a permanent or a periodic cure of the disease. Furthermore, the problem with inhibitor development will not be solved by gene therapy. Thus, for the foreseeable future, there is a need to

refine the prophylactic treatment of children with haemophilia. Today's prophylactic treatment, in my vision, should be developed to 'self-monitored and self-adjusted prophylaxis'. Measurement of factor (F) VIII and FIX concentrations should be possible with easy-to-use methods in the home setting in the same way as blood glucose in a child with diabetes mellitus. Depending on the planned activity, the factor concentration could be adjusted accordingly. A crucial prerequisite for such an approach is uncomplicated venous access allowing frequent injections.

It has been clearly shown that if FVIII or FIX is given at shorter intervals, the total consumption of concentrate may be reduced without resulting in a less protective prophylaxis [1]. Even in early studies, it was noted that scheduling short intervals between infusions was more important than achieving high peaks of plasma factor concentrations [2,3]. Thus, we need to improve venous access devices to allow frequent administration of concentrates to small children. The first option should always be to use a peripheral vein. If this is not feasible, another option is a central venous line, preferably an implantable venous access device such as the Port-A-Cath® [4–9].

As shown in Table 1, there seem to be two major experiences concerning infections, the most serious complication with central venous lines, in non-inhibitor patients. One is ≈ 0.2 infections per 1000 days [8,9] and the other ≈ 1.0 (range 0.7–1.6) per 1000 days [5,6,10]. Whether this is an acceptable frequency of infections for this group of patients depends on the situation and the treatment regimen for the individual patient. The child prone to spontaneous bleeds, who should start primary prophylactic treatment from the age of 1 year, is a greater challenge for venous access than the child receiving on-demand treatment with infrequent bleeds. The indication for a central line should be discussed with the parents, and the social situation and the need for home treatment should be taken into account when making a decision. The use of venous catheters in children were studied in the centres belonging to the European Paediatric Network for Haemophilia Management and it was found that in three out of 19 centres, > 50% of the boys under the age of six had a port while none had the device in seven out of 19 centres. A few children at some centres used ports after the age of 6 years [11].

Some groups report the use of peripheral intravenous access devices in children [P.A.S. Ports, SIMS, Deltec Inc., Slim-Ports (Bard)] [6]. These seem to be well accepted by the children and parents. In young children, it is less threatening to insert a needle in the periphery of the body and they can avoid the visible

Study	Number of patients (n)	Rate of infection per 1000 patient days	Comment
Blanchette <i>et al.</i> 1996	19	0.7	3 patients with inhibitors, 3 HIV+
Perkins <i>et al.</i> 1997	35	1.2 (central) 0.7 (peripheral device)	7/32 inhibitor, 2/32 vWD
Ljung <i>et al.</i> 1998	53	0.19	11 patients with inhibitors
Miller <i>et al.</i> 1998	41	0.14	Includes external
McMahon <i>et al.</i> 2000	58	1.6 (without inhibitor) 4.3 (with inhibitor)	77/86 devices Port-A-Cath®; 37/58 patients haemophilia

Table 1. The rate of infection in recent series with haemophilia patients using central venous lines [5,6,8–10].

profile of the port on the chest. However, peripheral ports have been associated with a higher frequency of thrombophlebitis and thrombosis, and the average time the patient may benefit from the device is probably shorter [6]. Another approach to venous access could be a modified version of the Percuseal® (device under development; Percuseal Medical, Husqvarna, Sweden) [12]. This device is implanted into the subcutaneous tissue, with the top portion protruding from the surface of the skin and enables administration without skin puncture in an attempt to combine the benefits from both an external and an implanted device. Continuous infusion of factor concentrates using portable pumps has been practised only on a short-term basis in haemophilic patients, and not for the purpose of prophylaxis, but may perhaps be a vision for the future.

The child with moderate or mild haemophilia

In a survey of 20 centres in Europe treating children with haemophilia, it was found that most children had severe haemophilia (52%) and only 29% mild haemophilia [11]. The proportion of mild haemophilia has been found in epidemiological studies to be 50–55% of the total haemophilia population [13]. The results can be interpreted either as mild haemophilia being underdiagnosed in some countries or more probably, many boys with mild haemophilia not being treated at haemophilia centres. For the future, a goal should be that boys with mild haemophilia should be registered and regularly seen by paediatricians at haemophilia centres. In this way, we can ensure that this group of boys receives the same quality of information, general treatment and optimal choice of concentrate as the boys with clinically severe haemophilia.

Another interesting group to discuss for the future are the children with moderate haemophilia (FVIII/IX = 1–5 U dL⁻¹). Some of these children have the same clinical manifestations as the boys with severe haemophilia (<1 U dL⁻¹), while some rarely bleed. On the other hand, approximately 10–15% of the boys with, by definition, severe haemophilia, have a low bleeding tendency [14]. What effect does having ‘a low bleeding tendency’ as a child has on joint function later in life? In the series studied by Petterson and coworkers [15], some patients already showed joint changes at the start of prophylaxis, although they had had no clinically recognized joint bleeds. This suggests that subclinical bleeds may trigger the development of arthropathy in children with only isolated clinical bleeds. In a country with a well-developed prophylactic treatment of children with severe haemophilia, the group at highest risk for bleeding complications, excluding the patients with inhibitors, are the ones with moderate haemophilia. Do we know if they slowly develop arthropathy that will be clinically manifested in adulthood? To be able to answer this question we need better instruments to monitor different aspects of joint status early in life.

New functional joint scoring systems for children

Today, most countries use the WFH approved orthopaedic scoring system and some also use a radiological scoring system (Petterson or Arnold–Hilgartner scales) [15,16]. However, these scoring systems were originally devised for the monitoring of mainly adult patients 20–25 years ago and they are not sensitive enough for the follow-up of the child with haemophilia today who is being treated more intensively. New joint evaluation systems have been

proposed by Manco-Johnson and coworkers, who expanded the WFH joint examination instrument to detect more subtle abnormalities of joint structure and function, and also suggested a new scale tailored to the dynamic growth and gait development of children [17]. The Child instrument in that study ($n = 43$) was significantly correlated to the WFH pain scale and was more sensitive to the performance capabilities of young children. A similar attempt has been made by the European Paediatric Network for Hemophilia Management (PedNet), which has two working groups charged with the tasks of developing new paediatric orthopaedic and MRI scoring systems [11]. Petrini and coworkers at the Karolinska Hospital, Stockholm, have in a small pilot study introduced a new orthopaedic scoring based on the practical experience as well as scores from the WFH scoring system (personal communication). Parameters such as swelling, muscle atrophy, crepitus on motion, and flexion contracture were diversified into three instead of two grades. Range of motion was subdivided by degree instead of percentage. Axial deformity and instability were replaced by gait and strength against gravity. Two more parameters were added describing a target joint and a joint with chronic synovitis.

The comparison of the original WFH scoring system and the new scoring system adapted for children, included a total of 116 haemophilia A and B patients aged 4–18, 56 of whom were on primary prophylaxis, 36 on secondary prophylaxis and 24 on on-demand treatment. The two scoring systems were applied to this patient population, stratified into three age groups, 4–8, 9–13, and 14–18 years. On primary prophylaxis, all except two children of the oldest age group scored zero in both systems. On secondary prophylaxis or on-demand treatment, the age-matched mean score evaluated by the new system was always higher (i.e. worse) than the score generated with the old system. The new scoring system reflected pathological alterations with a higher sensitivity and will thus be a better instrument to monitor the outcome of different therapeutic regimens to prevent joint bleeding and its sequelae.

New radiographic scoring systems for children

Radiographic scoring is another way to monitor disease progress in haemophilic arthropathy. Scoring using conventional radiography has been useful, but does not reveal early changes and minor progress of the disease [15]. Magnetic resonance imaging (MRI) has the advantage of visualizing changes in soft tissues of the joint not detected by conventional radiography system of haemophilia joints [18–21].

At this Congress, B. Lundin and coworkers, Lund University Hospital, Sweden, present a new MRI score with high resolution for progress of the disease and which separates, in the format A(e:s:h), the irreversible and reversible components of the arthropathy. 'A' represents the irreversible components of the arthropathy and the factors 'E', 'S' and 'H' represent effusion/haemarthrosis, synovial hypertrophy and haemosiderin, respectively. The ankles of haemophilic boys, 39 ankles in 29 boys aged 4–16 years (mean 10 years), were investigated with MRI, and classified twice by two experienced musculoskeletal radiologists. The results were compared for intraobserver and interobserver agreement by calculation of kappa values. The statistical analysis indicated a good intraobserver agreement and a moderate or fair interobserver agreement.

This work was carried out as a collaboration in the PedNet and the results indicate that MRI can be used as a more sensitive tool for early signs of haemophilic arthropathy than the conventional Pettersson radiological score [15,22]. A well-documented MRI score for haemophilic arthropathy has also been suggested by the Denver group. This score may be designated as 'progressive', i.e. progress is documented with a higher score only if a finding belonging to a more advanced level occur. The European score is 'additive', i.e. all findings influence the assessment, and the sensitivity for progress is higher. Depending on the aim of scoring, both systems have advantages and disadvantages.

The quality of life of children with haemophilia

If prophylactic therapy should be improved and more under the control of the child/parents, we would need only to evaluate joint status in order to find the strategy with the best cost–benefit or cost-effectiveness. The evaluation of quality of life of the child is the most important parameter to study. There are very few studies that evaluate the quality of life of children with haemophilia. An attempt has been made by a joint study between the haemophilia centres in Sweden, Denmark and Norway (A. Ozolins, Department of Social Sciences, University of Växjö, Sweden; personal communication). The series included 97 children on prophylactic treatment (mean age 11.5), 22 on on-demand treatment (mean age 11.6) and 992 age-matched controls (mean age 12.0). Boys on prophylactic treatment had 12.9 injections on average with factor concentrate per month compared to 3.1 for the on-demand group. The mean dose per injection was ≈ 200 U higher for the injections given on demand. These figures give a

rough estimate that this model of prophylactic treatment should consume four times as much concentrate as the on-demand regimen. On the other hand the prophylactic group had a mean of 3.7 reported bleeds year⁻¹ compared with 14.4 in the on-demand group and the mean orthopaedic joint score was 0.4 vs. 2.5. When asked 'are you a healthy boy?' there was no difference between the group on prophylaxis and the control group. However, the group on demand felt significantly 'less healthy' ($P = 0.03$). The boys with haemophilia (without differences between the treatment groups) scored higher than boys in the control group on 'intern locus of control', i.e. an adaptive sign (to disease and treatment) that they feel they have a better personal inner control of health. The prophylactic group seemed to ascribe their state of health, good or bad, more to fate and chance, which by experience from other disorders is usually a negative sign. A more detailed report of this study is in preparation.

To summarise, until gene therapy is a viable proposition, the treatment of children with haemophilia can be improved by introducing instruments for self-control of treatment and by developing better scientific instruments to measure various aspects of the outcome such as joint scoring and quality of life.

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