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Outcome in juvenile chronic arthritis

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In this talk I will present a conceptual framework for outcome studies, discuss methodological problems and summarise the knowledge we have today on outcome in juvenile chronic arthritis (JCA) from international studies. I will use the terminology juvenile chronic arthritis (JCA) and juvenile rheumatoid arthritis depending on what criteria have been used in the different studies I cite. The main areas that I will cover are:

? What is outcome?
? Methodological considerations
? Disease activity
? Disability
? Sequels/mortality
? Psychosocial outcome
? Conclusion

Spector and Hochberg (1) suggest a conceptual framework of outcome in epidemiological studies, derived from the *classification of consequences of disease* proposed by the World Health Organisation (WHO) (2). The same framework is also applicable to outcome studies of JCA. The impacts of disease are classified into impairments, disabilities, and handicaps outlined in Figure 1.

Figure1. The WHO framework for consequences of disease in the *International Classification of Impairments, Disabilities, and Handicaps* (2)

The disease can for JCA be described in terms of for example onset or course subtype, if it has early or late onset or whether it is still active or not. *Impairment* describes the consequence of disease at the organ level, for example in JCA joint scores and radiographic changes.
The definition of *disability* is "any restriction or lack (resulting from an impairment) of ability to perform an activity in the manner or within the range considered normal for a human being". *Handicap* is defined as the social consequences for the individual resulting from the impairment and the disability, for example the impact of the disease on school, activities and social life within and outside the family, and on employment.

While the disease process can be measured at a specific time , measurement of outcome also includes the suffering experienced throughout the duration of the disease.

Methodological considerations

Since we today do not know what causes childhood arthritis we cannot prevent it, nor do we have any specific treatment that eradicates the factors that perpetuate the disease process. In some cases the disease is self-limiting, while in others it is long-standing and destructive. Since our perception of outcome in this heterogeneous group of patients varies due to factors that are irrelevant to the disease process *per se*, we today do not know to what extent therapeutic interventions alter the outcome in the long-term perspective. When interpreting results in different outcome studies, three such methodological factors which influence our perception of natural history including the outcome of childhood arthritis evolve:

1) the criteria used for inclusion
2) patient selection
3) the method used for evaluating outcome.

The influence of these methodological factors must be minimized to make an analysis of interventions which may alter the outcome of childhood arthritis possible. Examples of such interventions are medical and physical therapy, psycosocial support and in relation to handicap, the value system of society, see Figure 2. The three methodological factors will be addressed separately in more detail.

Figure 2. Factors which influence our perception of outcome in JCA. On the left side the methodological factors which influences results in studies of outcome are presented and on the right side the factors which actually can influence the outcome for the patient are shown. The influence of the factors on the right side are difficult to evaluate because of the heterogeneity in outcome studies which are caused by the methodological factors on the left side.

1. Criteria

Chronic arthritis in childhood is a clinical diagnosis, since no "diagnostic tests" are available and the aetiology is unknown. Unfortunately, the criteria and the nomenclatures suggested in the late seventies in Europe (EULAR criteria) (3) and the USA (ACR criteria) (4) are not interchangeable, which causes confusion when comparison of studies are made. For example if 6 weeks is required for inclusion, as in the ACR criteria, more patients will have selflimiting disease than if 3 months is used as in the EULAR criteria. If onset subtype is used when evaluating outcome it will look different than if disease course type is used since roughly 30% of the patients will change subgroup during the disease course (5).

2. Selection of patients

When we meet a family with a child with newly diagnosed JCA, the question about the future prospects of the child always arises. For the family it will of course make a great difference whether we answer that the risk of severe disability is 3% (6) or 48% (7). This is the range we find in published follow-up studies with different selection of

patients! Thus, outcome studies should carefully address the implications of the patient selection , so we can interpret their meaning in relation to our own clinical settings.

Cases retrieved in a population based setting are representative of the population as a whole and include many mild and maybe transient cases, not normally encountered at a referral centre. Only a prospective population based incidence study can tell how many patients, who fit into the current criteria for JRA or JCA, will actually develop "chronic" disease and how many will have transient disease. The proportion of severely affected cases among hospital outpatients will vary according to referral patterns. Hospital inpatients are the most highly selected group of patients, since only few and usually severely affected patients are admitted for hospital care today.

Outcome can be studied in incidence or prevalent cases. The advantage with incidence cases is that there is less risk of selection bias and the cases are more representative of the disease as a whole. On the other hand incidence studies are more time consuming and many of the included patients will have transient or mild disease. I argue that in childhood arthritis further prospective studies of well defined subgroups of incidence cases are necessary to form base-line knowledge of the natural history and outcome. Such knowledge can then be used for comparison in prevalence studies in order to evaluate to what extent and in what direction patients are selected.

3. Methods for outcome evaluation

In JCA, disability or functional outcome has been evaluated using the crude *Steinbrocker functional* classification (8). This classification has been criticized for low sensitivity and lack of validity testing. New tools such as the *Childhood Health Assessment Questionnaire* (Child HAQ) have been developed to provide information according to the values of the patients. Now, CHAQ is one of the six components in the “core set of outcome“ used by the European organisation (PRINTO) for therapeutical studies in JCA.

So far, there has been no consensus as to which instruments to use to get more standardised and comparable results in the psychosocial dimensions of arthritis impact in paediatric rheumatology. However, the *Child Health Questionnaire* (CHQ), a quality of life instrument for children, is under validation in many European countries through PRINTO. In recent follow up studies of JCA patients in Norway several validated instruments were used, for example the Childhood Assessment Schedule (CAS), and Children’s Global Assessment Scale (CGAS) (9) .

Disease activity

There is still no international consensus on definition of active disease contra remission in JCA. One suggestion has been made by EULAR (in minutes from the meeting of the EULAR standing committee on paediatric rheumatology, Moscow, June 22, 1983): (a) active = increasing number of joints irrespective of drug therapy;

(b) stable = stable number of joints but requiring drug therapy; (c) inactive = no evidence of active synovitis and/or active extra-articular features and without drugs for less than two years; (d) remission = no evidence of active synovitis and/or active extraarticular features and without drugs for two years or more.
Others have used modified versions of the preliminary ACR definition of remission in rheumatoid arthritis where 5 or more of the following should be fulfilled for at least 6 months (irrespective of drug therapy); morning stiffness not exceeding 15 minutes, no fatigue, no joint pain, no joint tenderness, no swelling in joints or tendon sheaths, and erythrocyte sedimentation rate (ESR) less than 20 (10-11). None of these definitions, however, cover all clinical pictures. How do we for example define a patient with dry, contracted joints who has progressive loss of function and progressive radiographical changes but no active joints on examination? Or a patient who has no signs of active disease after six months but who requires heavy medication with potential long-term side effects to obtain that quiescence?

Laboratory data often fails to guide us in the evaluation of disease activity. In a Swedish epidemiological study a 7 year cohort follow-up was performed where we did find a correlation between disease activity and raised ESR or CRP at follow-up. Still, of the patients clinically classified as active or stable, 40% had normal ESR and 80% had normal CRP levels ! (12)

The proportions of patients with continuing disease activity, according to subgroups, and length of follow-up from studies performed in different decades and geographical areas, are summarized in Table 1. The figures show great variability, 16 to 44% (11, 13) of the patients in the pauciarticular group are reported as having continuing disease activity after 10 years of disease duration. In the polyarticular group, the range is 35 to 52% (11, 13). All the figures except the last two relate to the onset subtype and not the disease course, which may be one reason for the divergent results. Differences in the definition of disease activity may be another. In some studies, there is a tendency towards less disease activity with longer time of observation (13-14, 15). In contrast, Laaksonen found no such decrease (7). Selection bias could be one explanation, since the latter study is hospital based and the other studies emanate from referral centers including out-clinic patients. Since continuing disease activity is probably the most important factor for long-term outcome, further studies in defining risk-groups in this aspect are urgently needed.

Table 1. Reports on *continuing disease activity* at follow-up, in juvenile chronic arthritis by duration from disease onset and subtype.

Reference (Year) Follow-up period		Systemic %	Polyarticular %	Pauciarticular %	All subtypes %
Laaksonen 1966 (7)	3-7 years	-	-	-	41
	8-15 years	-	-	-	46
	> 16 years	-	-	-	41

Calabro 1968 (13)	7-10 years	30	52	44	43
Calabro 1989 (14)	25 years	1	7	1	9
Pedersen 1987 (6)	10 years	33	40	35	37
Ansell 1987 (15)	5 years 10 years	46 30	90 51	- 30	- 35
Michels 1987 (16)	5 years	54	61	76 (Type I) 33 (Type II)	44
Levinson 1992 (17)	>10 years	48	45	48	45
Andersson Gäre 1995 (12) *	7 years	-	55	29 (mono) 48 (pauci)	49
Flato 1998 (11) *	10 years	100	72** 35	16	40

*disease activity accordding to disease course type. ** pauciarticular onset, polyarticular course.

Disability

Reports on functional outcome evaluated by Steinbrocker functional classes are summarized in Table 2. Several explanations for the great variations can be suggested. The figures of Laaksonen (7) indicate that with longer observation periods, more patients will have an adverse outcome, 12% in class III to IV after 3-7 years and 48% after 16 years or more. However, that study was hospital based and was probably biased towards patients with more severe disease. The studies y by Pedersen (3) and Andersson Gäre (12) show the lowest proportion of patients in functional class III to IV, 3-5 %. Patients with localized, pauciarticular joint disease dominated in these studies, which indicates that more mild cases were included. On the other hand the follow-up is shorter in both studies then the rest, which may indicate that the proportion with severe disability will increase over time.

Table 2. Reports on functional outcome evaluated by Steinbrocker functional class in juvenile chronic arthritis by duration of follow-up.

Reference, Year		Years of follow-up (mean)	Steinbrocker functional class (%)		
			I	II	III-IV
Laaksonen (7)	1966	3-7	51	37	12
		16	10	42	48
Ansell (18)	1976	15	45	33	22
Pedersen (6)	1987	3-27 (10)	89	8	3
Calabro (14)	1989	25-37 (28)	-	-	15
Levinson (17)	1992	15-20	-	-	17
Andersson Gäre (12)	1995	2-22 (7)	55	40	5

During the last decade some studies of disability using patient questionnaires have been published. Mainly HAQ/CHAQ mentioned before have been used. Results from these studies are summarised in Table 3. All studies but the one by Andersson Gäre (12) find that roughly 40% of the patients experience some kind of physical disability after 15 years disease duration (19-20). The higher figure in the Swedish study, 60%, may be explained by the fact that only CHAQ was used which might be more sensitive than the HAQ in young adults. This is supported by Taal et al (21) who modified the HAQ for young adults by adding questions around ability to ride a bike, dance etc. He then found that only 85% had some disability in comparison with 54% if the HAQ was used.

Risk factors for disability were identified in logistic regression models in the above studies; continuos disease activity (11, 12), positive IgM RF, female sex (12), and high articular severity score (22). These findings again underline that trying to control disease activity must be the main goal in the treatment of JCA in order to hinder a continuos progression in physical disability. But, further studies to identify predictors on who will benefit from active medication early in the disease process are still warranted.

Table 3. Disability according to CHAQ/HAQ

Reference	Disease Duration Years	CHAQ/HAQ >0
Andersson Gäre 1995 (12)	7 (2-22)	60%
Ruperto 1997 (19)	15	42%
Peterson 1997 (20)	25	39%
Flato 1999 (unpubl)	>15	43%

Sequels and mortality

Growth and puberty

Delayed physical development as shown by growth and puberty may occur in all chronic disease in children/adolescents. Factors behind this in children with JCA are continuing inflammatory/disease activity, treatment with corticosteroids, reduced physical activity and nutritional factors. However, in the Swedish population based follow-up referred to before (12) no patients were stunted, which is in contrast to earlier findings where 0.4 to 53% of the patients were below the third percentile in height (7, 18, 23). Apart from the differences in patient selection, another possible explanation is the improved general health status in the population in recent decades, which may diminish the effects of chronic disease. Moreover, new treatment modalities and recent use of less long-term steroid treatment may influence the results. But, the earlier studies have a higher portion of patients with systemic and severe polyarticular disease where there still is a risk for stunted growth if disease activity can not be controlled. *Menarche* was not shown to be delayed either in population based or hospital based series of JCA patients (7, 12).

Local growth disturbancies occur in all subgroups of JCA. Involvment of temporomandibular joints, which occur in roughly 40% of JCA patients (24), can result in assymetrical growth or micrognatia. Leg length descrepancies have become less common after the active use of intraarticular steroids.

Uveitis

In population based series of JCA patients uveitis occur in 10-15%, with a predominance among pauciarticular arthritis (25, 26). The type is chronic in 1/3 to 1/2 of the cases. The prognosis in uveitis is worst in patients in whom the uveitis is diagnosed before or at the onset of JRA. In a recent Finnish population based follow up study of uveitis in JCA (median follow up 7 years) 1/3 had still active uveitis and 3 of them had complications. The overall visual prognosis has also become better with less than 5% visual loss. These figures contrast earlier reports from ophthalmologic clinics where more severe cases were selected and blindness was reported in 30-40%. The better prognosis during recent years can also be an effect of early ophthalmologic evaluation and proper treatment and the more active general treatment with for example methotrexate.

Amyloidosis

In earlier European reports the frequency of amyloidosis ranged from 3 to 7% (7, 27-28) . A decline in amyeloidosis during the last decade has been reported from Finland (29) which is supported by a study from Norway, 0.5% (unpubl, data) and a population based study from Sweden where no cases were found (12). Selection bias can again, account for part of the divergent results.. Modern treatment modalities aiming at reducing inflammatory activity introduced after the former studies were performed, and greater access to health care for the whole population in recent decades may have helped to lower the frequency of amyloidosis.

Mortality

In early studies mortality ranged from 4 to 7% (2, 27-28), while in reports from the nineties from USA the mortality was 0.3% and from England 0.9% (17). Mainly the

deaths have occurred in systemic onset disease. Amyloidosis and infections have been the most frequent causes of death. However, in highly selected series of patients, for example those who have undergone hip arthroplasty long term mortality rates have been very high 18-43 % (30-31).

Psychosocial outcome

Results from studies on psychosocial outcome in JCA are contradictory. On one side there seems to be good coping and little affection of the chronic disease and on the other there is a substantial negative impact of the disease. Again the selection of patients and the methods used for evaluation probably explain some of the discrepancies. In a Norwegian 10 year follow up of psychosocial factors were assessed by semistructured psychiatric interviews and standardised questionnaires. At folow up 17% of the patients fulfilled criteria for a psychaitric diagnosis nad 15% had mild to moderate impairment in psychosocial functioning. Psychosocial functioning was related to physical functioning in the patients below 18 years but unrelated to
other disease severity variables (11). In the 15 years follow up by Ruperto et al (19) patients reported high quality of life according to a standardised questionnaire (QOLS). However, the authors suspect that the instrument was not sensitive enough and suggest a multidimensional interview as a more rewarding method to gain further knowledge.

In a Swedish population based follow up of patients born 1968 to 1972 patients answered questions about school, professional plans and social life, their median age was 18 years (12). Generally, girls reported more influence of the disease on social life than boys did. A high CHAQ score, indicating physical disability, and continuing disease activity influenced school and social life more than sex or disease subtype. Girls had missed school more often than boys because of the disease 45 versus 21%, 32 % of the girls had missed more than 8 days during the last year. Girls also perceived that the disease had influenced their grades at school more often than boys, 57 and 45%, respectively.

In a population based study from Rochester, Minnesota of adults who have had JRA psychosocial outcomes and health status were compared with a control cohort. Average follow-up was 25 years. Greater disability, more bodily pain, increased fatigue, poorer health preception, and decreased physical functioning were reported by the cases compared with the controls. JRA cases also reported lower rates of employment but level of education, annual income, rate of pregnancy and childbirth were similar for both cases and controls (20).

In conclusion the field of outcome in JCA/JRA is very diverse, where the heterogeneity of the disease allows us to find support for both the paradigm that JCA is a self limiting disease and a progressive disease which creates disability and runs with a substantial mortality. It is important to put focus on the patients who suffer disease of the latter kind and find ways to identify them early in the disease course in order to use active treatment modalities before damage has occurred. But it is also important to give the necessary support to those who have milder disease to

diminish the risk for negative influence on physical and psychosocial development during childhood and adolescence.

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