ONCODEFI PROJECT

Cancer management in Persons with Intellectual Disability

Presentation of the Project

Project designers
Daniel Satgé MD, PhD
Projet ONCODEFI
IURC
Laboratoire Biostatistique
Epidémiologie Santé Publique (EA 2415)
641, avenue du Doyen G. Giraud
34093 Montpellier Cedex 5
Tel: +33(0)6 42 67 22 95
+33(0)4 77 33 26 07
daniel.satge@oncodefi.org
danielsatge@orange.fr

Bernard Azéma MD
Psychiatre - Conseiller Technique
CREAI Languedoc Roussillon
Montpellier
Tel: +33 (0)467 69 25 03
Fax: +33 (0)467 47 12 49
e-mail: bernard.azema@oncodefi.org

Stéphane Culine MD PhD
Oncologue médical
Service d'Oncologie Médicale
Hôpital Saint-Louis
1 avenue Claude Vellefaux
75010 Paris
Tel: +33 (0)142 49 42 47
Fax: +33 (0)142 49 98 95
e-mail: stephane.culine@sls.aphp.fr
stephane.culine@oncodefi.org

Introduction

1. Rationale for a center dedicated to cancers among persons with intellectual disability

The idea of taking up a project to create a center dedicated to cancers in persons with intellectual disability originated from an essential findings that **tumors are roughly as frequent in this specific population** as in the general population, but they are different on several counts and above all very poorly understood. Some conditions associated with intellectual disability are at high tumor risk for particular organs and tissues. On the contrary, other disorders seem to protect against cancers which are frequent among the general population. Some conditions have an unusual tumor profile, to be known in order to ensure a better cancer care. Additionally, some cancers, for example digestive tumors, are overrepresented in the whole group of persons with intellectual disability asking for an appropriate surveillance. Incidentally, persons with intellectual disability have, apart from risk factors they share with the general population, cancer risk factors of their own.

The intellectual disability condition is a source of **great difficulties** for **diagnosis and management,** partly because of the intellectual handicap and partly due to some biological particularities which make it necessary to reconsider the treatment. Anesthetic, surgical managements, chemotherapy cures and radiotherapy sessions have to be appropriate. **Therapeutic means have to be often adapted** on specific criteria.

As life expectancy of persons with intellectual disability increases, cancer represent, currently, a significant burden for them. Health professionals who provide care for these persons are unfamiliar with cancers and their treatment. Medical and scientific data on the subject are quite scattered and often hard to get. We have started to overcome this difficulty in a book devoted to cancers in persons with intellectual disability [Satgé et Merrick 2011].

These are the different reasons that have made us wish for **treatment teams** articulated with **a research core,** associated with a **documentation center,** for persons with intellectual disability, via their family members, carers and health professionals. An oncology group must be set up that will be specifically devoted to the treatment of cancer in persons with intellectual disability and will serve also as a **reference and resource center**. Epidemiological studies have to provide a precise idea of the frequency of cancers, as well as risk factors that need to be known for screening and prevention. Then, useful information must be made available in a fitting and progressive manner to patients, their families and the nursing staff as well as to cancer teams in France and abroad. Finally, good practice guidelines are to be devised, developed and disseminated.

In the first part, we present ONCODEFI project in its broad outlines. The second part provides general indications on cancers in persons with intellectual disability. They are largely taken from a chapter of the book on the subject written by the authors of the project [Satgé et al 2007].

Description of ONCODEFI project

2. Composition of ONCODEFI group

The objective of ONCODEFI is to enable intellectually disabled persons of all ages to get an **easy access to current therapeutics against cancer.** This includes prevention at its different levels, screening if necessary, and different therapeutic stages.
It involves:

- The creation of specialized, therapeutic, oncologic reference teams, which will be the main focus of the project.
- Linked up with a documentation and bibliography monitoring center.
- In conjunction with an epidemiological, psychological and biological research core.

3. Cancer treatment team for persons with intellectual disability

The main objective is to set up three teams. These teams will be empowered to carry out the treatment of malignant conditions in persons with intellectual disability in the Beau Soleil Clinic, the University Hospital and the Cancer Hospital Val d'Aurelle Paul Lamarque, in Montpellier.

The setting up of such teams is justified by the great difficulties that arise in a current oncologic team from the management of persons with intellectual disability. These difficulties are psychological and relational in nature, requiring a flawless professionalism. These difficulties are also medical and scientific in nature, demanding a thorough knowledge of the biology of various conditions responsible for intellectual disability, in different stages of diagnostic and therapeutic course. Difficulties are explained in detail in the paragraph "treatment" in the second part of the project and particularly in a publication of the organizers of the project [Satgé et al 2007].

It is proposed to accompany the person with intellectual disability all along his/her diagnostic and therapeutic course by setting up **appropriate structures and reception modalities** as well as an optimal environment. This will provide necessary means for the treatment of malignant conditions taking into account the specific needs of social and psychological support.

Therapeutic teams have to face a complex situation wherein particular oncologic issues are associated with psychological and sometimes behavioral difficulties. Communication possibilities, limited by intellectual disability, difficulties in obtaining an informed consent, the willingness of the patient and/or the willingness of the friends and family for the treatment, help from the natural or professional helpers are as many sources of complexity.

The group has to get associated with
-a motivated oncological (medical and paramedical) team
-a social and medico-psychological support team
-securing help from family members and usual helpers of the person for **preserving at the maximum level his/her expressive and communicative skills.**

Biologically, for each particular condition (that is, for each syndrome and possibly the sub-groups of these syndromes, in case they exist), health care teams must adapt methods of treatment to the patient’s physiological reality and to the state of Science, in the best possible manner. Does anesthesia involve particular risks? Has it to be modified? Is surgery acceptable? Is the patient’s body able to withstand a radiation therapy? Is chemotherapy feasible? If so, should it be developed? Does the patient suffer? What means have been

developed to assess his pain? And how to treat it? And in the event of adverse developments in the disease, what arrangements have been made to give the patient the end-of-life care? The fundamental point for all these decisions is that they should not be taken on the basis of vague notions and impressions difficult to verify. **Decisions should be solidly based on well-established scientific and medical notions and on experiences clearly gathered from similar situations.** Here the role of a flawless documentary monitoring is extremely important.

Thus, following these principles, reference teams will acquire the competence to establish protocols of care adapted to each type of patient, to each disabled condition, and according to different groups of malignant tumors. These teams can help therapeutic teams in other hospitals by sharing their knowledge and experience with them.

4. Documentation and bibliography monitoring center

The goal of the documentation and bibliographical monitoring center **is to gather all validated data concerning tumors in persons with intellectual disability,** classify and coordinate them so as to make them available for patients, their families and oncology teams. The Center is conceived as a resource place of available information at the national and international levels.

Such a **Center is the need of the hour** since currently no documentation structure or site providing this role exists in France or abroad. The problem of cancer among persons with intellectual disability is a complex one. It involves detailed knowledge of genetics, molecular biology, cellular physiopathology, hematology and oncology, cancer biology, psychology and management of intellectual disability, pharmacology, prevention and screening.

There is a great wealth of documentary data, but which are widely dispersed and sometimes hard to access. They could come from medical articles in very specialized reviews, some of which are available only abroad, monographs and books scarcely distributed and hardly known, but highly informative [Hogg et al 2001, Tuffrey-Wijne 2010] on pathologies in intellectually disability. Our experience over twenty years of literature monitoring and a collection of documents in the field allows us to observe that even the most important are fragmentary. They are often included in articles dealing with other subjects. For example, the experience concerning patients with an intellectual disability condition is related in an article on tumor treatment of a given cancer. The gathering of all these information, once coordinated and analyzed, will be an impressive mass of valuable data. The first stage of the work is available in a chapter prepared by the organizers of the project [Satgé et al 2007].

The Center must be supplied with productions of medical, scientific and psychological literature in all its potential extensions. It will actively collect experiences of teams involved in the oncologic care of such patients. It will gather the results of epidemiological, biological, pharmacological and psychological works not yet made available in literature, but validated in the field. The center will network with formalized data bases, like ORPHANET on rare diseases which supplies very important information to practitioners, families and any other research or university organization. It will establish partnerships with French and foreign teams and researchers.

The data are meant for:

1. Patients and families through a general access so that they may easily obtain informations and useful contact.

2. Professionals in the field of intellectual disability, through a proper and safe access.
3. Medical profession, through a clean and safe access, chiefly the teams which take care of patients with an intellectual disability and which are anxious to practice a medical supervision as relevant as possible in terms of oncology.

The Center will gather international experience whenever it is available, will build up and spread follow-up protocols as expertise and capitalized experience progress. This will concern particularly vulnerable conditions to cancers or, in an equally useful way, syndromes in which cancers are the most rare. The data will be devoted also to oncology teams which take care of patients affected with an intellectual disability but which have no particular experience with patients with mental retardation

With all this equipment the Center will help better to understand the frequency and the distribution of tumors, their characteristics in different conditions associated with intellectual disability. It will help to validate appropriate protocols of surveillance or screening, and concerted therapies. It will aim to provide a well adjusted care, without under or over-medication of patients. The data, once collected and organized, will also be a source of thinkings to encourage research work in epidemiological, psychological and biological fields.

5. Epidemiological, psychological and biological research

Epidemiological Research

Epidemiological research is fundamental for understanding and improving the management of persons with intellectual disability suffered from a cancer, since the screening and prevention stage up to treatment and during follow-up before and after treatment. The knowledge of different types of cancers observed in different conditions, whether genetic or not, that is, the tumor profile of diseases with intellectual disability is still in the embryonic stage. Studies started for Down syndrome, the best-known of them today, for fragile X syndrome and also for cerebral palsy. But in many disorders little is known about which **organs are at risk and the degree of that risk**. Digestive tumors are frequent among persons with intellectual disability. However, the true frequency of each tumor type and **risk factors** must be analyzed more deeply for a better follow-up (gastro esophageal reflux, *Helicobacter pylori* infection, hepatitis B infection, cholelithiasis, constipation, overweight etc.). The effect of medical treatments on risk factors and the protective role of physical activity are important to know for prevention. Finally, the best criteria and the best **modalities of surveillance and screening** have to be determined, on the one hand, for the global population of persons with intellectual disability, on the other hand, for some specific conditions. We know that persons with intellectual disability having the same particular genetic syndrome are not all equal for tumor risk which may vary with the specific type of molecular disorder that causes the disease.

We wish to set up **an exploratory survey at regional** and inter-regional levels. One first phase of the research will consist of a questionnaire surveys in institutions on reported cases of cancer during the last 5 years among persons with intellectual disability. This survey will rely on the knowledge and expertise of the CREAIs teams (Centres Régionaux pour Enfants et Adultes Inadaptés) (Regional Centers for Disabled Children and Adults). This questionnaire survey will be supplemented by on-site meetings with health care professionals and care providers, respecting ethical and deontological rules. Languedoc Roussillon will be the test region for the feasibility study of this type of survey. The Languedoc Roussillon CREAI will lend methodological and logistic supports to this questionnaire survey.

Based on information gathered during this first phase, a **national** or multi-regional survey will be conducted. It will rely on the knowledge acquired and will aim to draw more ambitious outlines for the studies on prevalence and incidence.

This national survey will rely on **the international network** developed on our initiative with researchers of the International Association for the Scientific Study of Intellectual Disability IASSID (Website: http://www.iassid.org/). This network brings together worldwide researchers working within the area of intellectual disability.
IASSID is the WHO's expert association in the field of intellectual disability. Some researchers from Netherlands, Finland, Ireland, the UK and Israel have already shown interest in this approach and have already started working on these health problems. Other promising contacts are with *POMONA* European group network, to which one of us (BA) belongs to, and which works on health indicators for persons with intellectual disability http://www.pomonaproject.org/index.php).

Finally other difficult and lengthy ongoing surveys could be activated and conducted in a speedup way in the context of a reference center which could include students such as international studies on the frequency of solid tumors in Down syndrome, fragile X syndrome and in other conditions for example.

Medico-psychological Research

Persons with intellectual disability have specific psychological and behavioral features, often disrupted means of adjusting to the environment, difficulties to express themselves and to understand. The occurrence of a serious physical and existential crisis represented by the discovery of cancer and its treatment requires specific and tailor-made approaches [Tuffrey – Wijne, 2010].

These specific approaches are related to the ability of these patients to communicate with a new entourage, their own access and their understanding of the disease and therapeutic constraints, their ability to express their pain and their aptitude to assess it and alleviate it. Finally, it is sometimes extended to the end-of-life support and palliative care to be offered [Dusart 1988, Tuffrey-Wijne et al 2007]. The interaction of the person with an intellectual disability with his or her entourage in these circumstances is not totally elucidated and some aspects have to be studied in-deepth. The research concerns, of course, the disabled person himself (or herself) in a difficult condition, but also health care teams , as pointed out by studies already undertaken in the field [Hendren et al 1990, Hennequin et al 2000, Black and Hyde 2004, Tuffrey –Wijne et al 2006, Hanna et al 2010].

One objective will be to **define health course typologies** and the needs of persons with intellectual disability. For these persons, patterns of use of prevention, screening, diagnosis and treatment differ according to the person and the existing offer. Accordingly, based on typologies of courses and needs, it will be possible **to build up strategies of clinical care better adjusted** to meet the specific needs.

Biological Research

One major objective is **to generate and to test hypotheses of biological research** prompted by epidemiological data and clinical and therapeutic observations. Hypotheses may originate from observations on results of epidemiological surveys showing variations of tumor frequency in some conditions with intellectual disability. They may concern the biological impact of risk factors in a particular organism. Clinically, they could also be prompted by the unusual observations on the disease progress and patients response to cancer treatment. **The**

group will have a privileged position, it will add a specialized high level clinical experience to an updated, unique and extended documentation in the area of constitutional genetics of oncology. It will thereby gather the best conditions to be in a position to produce original thinkings based on actual data, characteristic aspects of cancers in intellectually disabled conditions. The availability in the same site of epidemiological work, and literature monitoring aiming to organize, structure and synthesize the data and clinical expertise, provides the best conditions for an original thinking and a renewed approach of cancer in the area of intellectual disability hitherto very little explored.

This is how we have already proposed the possibly anti-tumor role of protein S100B to explain the rarity of central and peripheral nervous tumors in Down syndrome. We have also suggested the protective role of tissue over-maturation to explain the decreased frequency of some tumors [Satgé et al 2007]. We have also put forward the hypothesis of the protective role of extra-cellular matrix to explain the rarity of mammary tumors among patients with Down syndrome. Preliminary experiments confirm this hypothesis [Bénard et al 2005, Satgé and Bénard 2008]. More precisely, this type of study group on cancers in intellectual disable patients will help to explore a phenomenon that has been little studied and little known, i.e, natural resistance to cancer. Some constitutional disorders result in a decreased frequency of some cancers, witnessed in Down syndrome and fragile X syndrome. Some cross-sectional analyses of groups of intellectual disability showing some common characters and which seem protected against some types of cancers will even suggest hypotheses. Our work will be also thinking up simple biological experiments to verify the hypotheses.

Epidemiological, biological and pharmacological researches amongst persons with intellectual disability will contribute to a better knowledge of cancer in the general population.

Intellectual Disability

6. Intellectual Disabilities

The reader who is familiarized with these notions may directly go to the paragraph on cancers. (7)

Definition, frequency and classification

Intellectual disability results from the association of significant limitations in intellectual functioning with significant limitations in adaptive functioning, at onset prior to age 18 years [Garcin 2003].

Among the general population 3% of persons have an IQ below 70. One third of them show also significant limitations of adaptive behavior. The prevalence of intellectual disability is estimated to be 1% of the general population in industrialized countries. On these bases, intellectual disability affects 600,000 persons in France, about 4,500,000 persons in Europe, and 3,000,000 in the USA. The overall world population of persons with intellectual disability is probably over 60 million since in some countries on the way to industrialization like India and Pakistan, the prevalence is definitely higher, reaching 8% of the population in the region of Karachi in Pakistan [Durkin and al 1998]. The sex ratio is estimated around 1.6 boys for 1 girl [Tassé and Morin 2003].

The great majority (about 80%) of persons with intellectual disability have a mild deficit according to the WHO, their IQ ranging from 70 to 55. Moderate intellectual disability (IQ between 55 and 40) represents 15% of the total. Severe intellectual disability (IQ between 40 and 25) and profound intellectual disability (IQ below 25) account for only 5% of the whole group. In specialized services, patients who have mild, moderate, severe/profound intellectual disability account respectively 50%, 35% and 15% [Tassé and Morin 2003].

Etiologies of intellectual disability

About 15% of intellectual disabilities have a genetic, chromosomal or gene origin. Prenatal, neonatal and postnatal causes cover about 35% of the patients. Environment-linked origin is suspected in 20% of cases of intellectual disability. At least 30% of cases of intellectual disability are not characterized [Tassé and Morin 2003, Jeanpierre 2004]. The most marked disabilities have four out five times a recognized genetic or prenatal origin [Gillbert and Sodestrom 2003].

Genetic Causes. Down syndrome is the most frequent chromosome anomaly, accounting for about 10% of all intellectual disabilities. It is followed by other complete trisomies (8, 9, 13, 18), often as mosaicism, partial trisomies, tetrasomies (12p, 18p, 22q), and deletions. Microdeletions, for example, di Georges syndrome (microdeletion 22q11), and subtelomeric microrearragements account for a significant proportion of undiagnosed cases [Rehder and Fritz 2005].

Gene causes are represented by nearly 2,000 syndromes associated with intellectual disability. An important phenotypic variability is observed [Henderson et al 2004]. Recessive autosomal anomalies are for example microcephaly, inherited diseases of lysosome metabolism (mucopolysaccharidoses, gangliosidoses…), aminoacidopathies (phenylketonuria, for example) and various degenerative conditions of CNS. There are also dominant autosomal anomalies such as type 1 neurofibromatosis, tuberous sclerosis or Steinert's disease, which are not always associated with an intellectual disability. On the contrary, intellectual disability is systematic in other most rare syndromes, like Rubinstein-Taybi syndrome [Miller and Rubinstein 1995] or Cornelia de Lange syndrome [Sugita et al 1986]. Finally, a series of intellectual disabilities results from sex-related genetic diseases. About 60 different types have been identified, among which fragile-X syndrome is the second genetic cause of mental retardation after Down syndrome [Jeanpierre 2004]. The latter group resulting from mutations on chromosome X explains in part why boys are more often affected by intellectual disability than girls [Gillbert and Sodestrom 2003].

Prenatal, neonatal and postnatal causes. The brain of the developing fetus can be altered by maternal infections such as rubella, cytomegalovirus infection, toxoplasmosis or HIV infection. The brain can suffer also from poisoning by mercury which is found in excess in some contaminated foods or polychlorate substances. A maternal treatment, e.g. an antiepileptic treatment (valproic acid), thalidomide, excessive maternal consumption of alcohol, drug taking by the mother or irradiation between 8^{th} and 15^{th} week of pregnancy may also alter fetal brain development [Gillbert and Soderstrom 2003, Tassé and Morin 2003, Jeanpierre 2004].

At birth, a cranial traumatism, a neonatal hyperglycaemia, serious intracerebral bleeding, a prolonged asphyxia or a viral infection (herpes virus for example) may end up in an intellectual disability [Holst et al 1989, Jones 1997]. Low-weight or premature newborn

babies are also at increased risk of intellectual disability [Marvis et al 1995, Gillberg and Soderstrom 2003].

After birth, head injuries, infections (meningitis, encephalitis) [Durkin et al 1998], lead poisoning, e.g. from old pipes [Jones 1997, Jeanpierre 2004], unrecognized and untreated hypothyroidism are also responsible for intellectual disability.

Other causes. Environmental causes are often linked to poverty and are principally responsible for mild intellectual disabilities [Durkin et al 1998, Gillbert and Soderstrom, 2003, Tassé and Morin 2003]. Etiological factors are often interlinked, combining phenomena related to malnutrition, with a lack of physical and sensory stimulation and a lack of care. According to some authors, an unfavorable cultural environment is rarely the exclusive cause of intellectual disability.

The sub-group of unknown causes is chiefly made up of mild intellectual disabilities that may result from entangled factors. It is also likely that some genetic causes are not yet identified.

Pathological associations. In a large number of persons, intellectual disability is associated with congenital malformations, cerebral palsy, autistic manifestations, epilepsy, sensory impairment or mental illness [Gillbert and Soderstrom 2003, Azéma and Martinez 2005].

Cancers and Intellectual Disability

7. General frequency of cancers in intellectual disabilities

Cancer frequency in persons with intellectual disability is difficult to assess, because this topic has been barely explored [Hogg et al 2001]. Two recent surveys on prevalence, specifically devoted to cancers in persons with intellectual disability in Finland [Patja et al 2001] and in Australia [Sullivan et al 2004] suggest an **incidence comparable to that in the general population**. For the first, covering the period 1967-1997, and concerning persons with various levels intellectual disability, the standardized risk (SIR) was 0.9. But the breakdown by types of cancer differed from that of the general population [Patja et al 2001]. The second survey, conducted in Western Australia, in persons with various levels of intellectual disability, and also institution based or community based, found out 200 cancers in a period of 20 years. In that group the standardized incidence rate per age bracket was similar to that of the general population, i.e. 1.14 for men and 1.01 for women [Sullivan et al 2004].

8. Age- specific frequency

Children and Adolescents (0 – 19 years)
The Australian survey [Sullivan et al 2004] indicates an increased standardized risk (SIR) for both sexes during the first four years of 7.23 (IC 4.04 – 11.92) for boys, and of 6.37 (IC : 2,64 -13,53) for girls. The risk decreases later between 5 and 19 years to reach the unity. **An increased cancer risk at a very young age for some conditions** is expected since in

constitutional conditions associated with an increased cancer risk and intellectual disability, the onset of cancer is more precocious [Isaacs 1997, Bishop 2004]. This is the case for genetic disorders wherein intellectual disability is occasional, such as type 1 neurofibromatosis, in which cerebral tumors and leukaemia appear as early as childhood and adolescence [Narod et al 1991, Guillamo et al 2003]. The relative risk for all cancers before the age of 15 was estimated at 16.3 in this condition [Narod et al 1991]. This is also the case for diseases in which intellectual disability is more frequent, like tuberous sclerosis [Al-Saleem et al 1998], with a relative risk for all cancers before the age of 15 estimated at 18.1 [Narod et al 1991]. This is also the case for genetic disorders such as Down syndrome in which intellectual disability is systematic. In Down syndrome between 0 and 4 years the relative risk for leukaemia has been estimated at 56 in Denmark [Hasle et al 2000] and at 17.4 for all cancers in a Norwegian study [Windhan et al 1985]. It must be added that many rare or very rare genetic syndromes with intellectual disability have a high cancer risk in early childhood. Besides intellectual disabilities of genetic origin, fetal alcoholism syndrome is responsible of cancers diagnosed mainly before the age of 6 [Kiess et al 1984]. In cerebral palsy, which is sometimes associated with intellectual disability, deaths from brain tumors before the age of 15 have been estimated 26 times more frequent than in the general population [Strauss et al 1999].

Adults, (20 to 59 years)

The oncologic risk observed during the childhood decreases and stabilizes for adults at a level equivalent to that of the general population. This is shown in both the Finnish and the Australian surveys. Between the ages of 30 and 59, 69 cancers in adults with intellectual disability had been identified in the Finnish Cancer Registry for the years 1967 to 1997, whereas 68 were expected [Patja et al 2001]. Meanwhile, the Western Australia Cancer Registry identified 132 cancers in men and women with intellectual disability between the ages of 29 and 59 over a period of 20 years, whereas 130 were expected [Sullivan et al 2004]. These data suggest a risk similar to that in the general population for the group as a whole. However, variations in the direction of increase or decrease are to be considered for particular groups of patients. Accordingly, in Down syndrome, a risk reduced by half was shown for solid tumors between the ages of 30 and 60 [Hasle et al 2000]. On the contrary, in Cowden syndrome which is accompanied by intellectual disability in 10% of patients, breast cancer risk is highest in the third and fourth decades [Eng 2004]. While waiting for additional data, it appears currently that the overall cancer risk among adults with intellectual disability is similar to that in persons without intellectual impairment.

Persons aged 60 and above

The overall life expectancy of persons with intellectual disability is not likely to reach that of the general population to the extent that some groups of persons succumb early to various disorders of their own, such as cardiac malformations or respiratory accidents favored by mobility restriction [Azéma et Martinez 2005]. Life expectancy of persons with Down syndrome has much progressed, but remains lower than that of general population [Strauss et Shavelle 1998]. After the first few years of life with intellectual disability, the more the years go by, the more the mortality rate is closer to that in the general population [Azéma et Martinez 2005]. Thus, an increasing number of persons with intellectual disability will reach and goes beyond the age of 60. In the Finnish survey [Patja et al 2001], a group of 198 mostly community based persons were followed for 30 years and 104 among them (48 men and 56 women) developed a cancer. For men the standardized risk by age was significantly reduced by about one third (SIR = 0.7 with a confidence interval (CI) from 0.5 to 0.9). For women, it was equal to that of general population (SIR=1). In the survey conducted in Western Australia

[Sullivan et al 2004], 35 cancers affecting 19 men and 16 women above 60 years of age were identified although 46 were expected. This moderate decrease, more pronounced for men, was not statistically significant. Finally, two studies were conducted on institution-based persons above the age of 60, who had half of them a severe to deep mental retardation. The first one, conducted in the US, has identified 52 cancers in 347 persons of which 33 were women (20%) and 19 were men (10%) [Janicki et al 2001]. The second, conducted in Israel [Merrick et al 2004], has identified 17 cancers among 274 persons i.e. 11 women (8% of women) and 6 men (4% of men). The low values of these two surveys are probably related to a high proportion of patients with severe and deep intellectual disability, which are less vulnerable to cancers.

9. Frequency according to the severity and origin of intellectual disability

The overall frequency of cancers according to the severity of intellectual disability has not been established precisely either. **Earlier studies found a lower risk for the most important disabilities.** An old Scottish study in which patients were divided into three groups found 4% cancer deaths for deep disability against 9% and 15% for moderate and mild disability respectively [Primrose 1966]. In Texas, another mortality survey found 3% of cancer deaths in the group of patients with deep and severe disability against 8% and 9% for mild and moderate intellectual disability [Achtenberg et al 1978]. More recently, in California, cancer deaths were also less frequent for deep intellectual disability compared to mild, moderate and severe disabilities [O'Brien et al 1991]. An incidence study conducted in Finland does not show a statistically significant difference between levels of intellectual disability, irrespective of sex [Patja et al 2001]. A reduced risk for the most marked intellectual impairments is yet to be confirmed and quantified.

Cancer distribution in organs varies according to the level of disability. Persons with deep disability develop more testicular cancers (9.9 times more than the general population), more gallbladder cancers (10.3 times more) and more cerebral tumors (3,5 times more) [Patja et al 2001]. A study of esophageal carcinoma also showed an increased risk for patients with an IQ lower than 35 [Böhmer et al 1997]. On the contrary, the risk of cancers in the aero digestive track and bronchi is significantly reduced in the group of deep disability compared to the mild and moderate ones. This is related to a less tobacco consumption in deep disability [O'Brien et al 1991, Patja et al 2001, Sullivan et al 2004].

The knowledge of the tumor profile of the most frequent disorders is increasing progressively. Down syndrome favors strongly leukemias and gonadic and extragonadic germ cell tumors [Satgé et al 1998, Hasle et al 2000]. Type 1 neurofibromatosis favors cerebral tumors and leukaemias [Narod et al 1991]; tuberous sclerosis increases the risk of renal and cerebral tumors [Al-Saleem et al 1998]. In Costello syndrome, rhabdomyosarcomas and excreto-urinary tumors are particularly frequent [Gripp 2005]. Intellectual disability due to inherited metabolic diseases are often associated with cerebral tumors, hepatic tumors and leukaemias [Satgé and De Lonlay 2010]. For many other conditions, the tumor risk is not well kown. And the type of tumors particularly at risk has not yet been determined.

Finally, it must be born in mind that some condition with intellectual disability seems to be protected from cancers. This is the case in fragile X syndrome, for which few tumors are reported in literature. An epidemiological survey on 223 men using the Danish Cancer Registry has shown, with a relative risk of 0.28, a reduced frequency of cancers compared to the general population [Schultz-Pedersen et al 2000]. These important variations according to the genetic condition indicate that the oncologic surveillance of patients with intellectual

disability will be all the more effective and adapted as the tumor risk for each condition of disorder is better known.

10. Organ-specific distribution of cancers

A description of cancer distribution according to the organs and tissues is given in detail in a chapter on cancer in intellectual disability written by the organizers of this project [Satgé et al 2007].

Overall **three groups of cancers can be distinguished** among persons with intellectual disability. *The first group* is the cancers favored by the condition responsible for intellectual disability. Thus, Down syndrome favors leukemia and testicular tumors [Satgé et al 1998], neurofibromatosis type 1 favors cerebral tumors [Guillamo et al 2003]. *The second group* is the tumors common to all conditions of intellectual disability. This is particularly true for tumors of the digestive tract. This group is incompletely defined at present. *The third and last group* are the tumors observed in the general population and which result from the interaction between the genome and the environment. They can affect persons with intellectual disability as any other member of their family.

Cerebral tumors are more common in patients with intellectual disability. **Digestive tumors** affecting particularly esophagus, stomach, colon and also liver and gallbladder are more often diagnosed. Breast cancer which is the leading cancer in women is as frequent (excepting Down syndrome) as in the general population. Ovarian cancers are probably a little on the increase. Cancers of the cervix that have sexual intercourses for essential risk factor are very less frequent. Unfrequent are also urinary tumors affecting kidneys and bladder, even if few syndromes with intellectual disability favor them.

Testicular tumors are found more frequently, and not only in Down syndrome [Sasco et al 2008]. There is also a probable excess of thyroid cancer, of eye cancers, and of lymphomas. Skin cancers appear very less frequent.

These preliminary data have to be backed up and quantified by more specific and targeted epidemiological analyses.

11. Oncologic risk factors in intellectual disability, prevention and screening

As persons with intellectual disability share the same environment, they are exposed, excepting professional situations, to the **same risk factors** favoring cancers. However, the relative importance of these factors varies much with the mode of life in institutions or in the community, therefore according to the level of disability. Less tobacco and alcohol consumption, reduced sexual genital activity and scant exposition to the sun reduce the risk of cancers of upper aero-digestive tract and bronchus, cervix and skin. On the contrary, constitutional disorders that favor obesity, gastro-esophageal reflux (increased by antiepileptic and other CNS drugs) favor digestive organs carcinogenesis. A higher prevalence of *H pylori* infection and higher incidence of hepatitis B increase the risk of gastric and hepatic cancers in these persons.

Genetic risk factors are prominent in a large number of conditions such as Down syndrome, Beckwith-Wiedemann syndrome, tuberous sclerosis. The type of genetic disorder for the same syndrome may condition both the importance of oncologic risk and the level of intellectual disability. The tumor risk is often more marked in case of chromosome microdeletion compared to gene mutation for example in type 1 neurofibromatosis and Sotos syndrome. Thus, oncological surveillance will vary according with the genetic mechanism.

Finally, it must be born in mind that in **a cancer family**, the oncological risk applies also to the family members who have an intellectual disability. He or she needs to be monitored, as far as possible, similarly to other members of the family.

Primary prevention will try to reduce *H pylori infection*, provide surveillance and treatment of gastro esophageal reflux and **vaccinate against** hepatitis B. Tobacco and alcohol consumption in mild disability should be reduced through an appropriate education [MacCusker et al 1993, Tracy and Hosken 1997].

A planned oncologic surveillance of patients with syndromes at risk of cancer has been proposed for Williams syndrome [Thomburg et al 2005], Costello syndrome [Gripp 2005] and Beckwith-Wiedemann syndrome [Tan et Amor 2006]. This approach should allow an earlier diagnosis, and therefore most light treatments. Thus, it would be judicious to establish monitoring programs, at least for the most frequent groups of intellectual disability having a high carcinogenic risk. Persons with intellectual disability should benefit from cancer screening available for persons of the general population. This is far from the case for breast cancer [Piachaud and Rohde 1989, Davis and Duff 2001], although these tumors are as frequent as in women without intellectual disability. Women who suffer from severe intellectual and physical disabilities are less well monitored [Sullivan et al 2003]. This leads to later discovery of tumors in an advanced, even metastatic stage, difficult to treat, sometimes beyond therapeutic resources [Verger et al 2005]. In other cases, on the contrary, we must know to do not screen as it is done in the general population. Routine mammograms are questionable in women with Down syndrome having a low risk of breast cancer [Satgé et al 2001**,** Satgé and Sasco 2001]. In the same way, screening with Pap smear must be reconsidered if it is sure that a woman has no genital sexual intercourse. **All these features should be thoroughly known for an optimal monitoring.**

12. Cancer treatment in persons with intellectual disability

Difficulties in treating malignancies in persons with intellectual disability are due to tumors observed at a late stage, to limited cooperation of patients as a result of their difficulty in understanding and communicating, and to physiological characteristics specific to some conditions.

Some cancers are sometimes discovered at a very advanced stage with local disrepair, even revealed by metastases [Kustner et al 1993, Tuffrey Wijne 1997]. The patient may deliberately conceal his disease [Tuffrey Wijne et al 2007].

It is really very important **to involve the patient in his/her treatment** by giving him/her necessary information in an appropriate manner [Donagey et al 2002, Réthoré 2006]. Healthcare providers will not be able to obtain the active cooperation of a patient if he/she has not understood the whole issue in general terms. Communication difficulties are prominent between the patient and oncologic teams who are not familiarized with persons with intellectual disability. This is particularly true for deep and severe disabilities [Hogg et al 2001]. For example, a patient may give his/her informed consent to a therapeutic proposition without grasping the whole issue, and without asking details necessary for understanding [Black and Hyde 2004]. Even healthcare teams attending to persons with intellectual disability may feel powerless while dealing with a handicapped patient with a heavy malignancy [Hendren et al 1990, Bycroft 1994]. However, keeping pain under control, assessments of symptoms, on the healing follow-up after a surgical intervention are crucial for monitoring the patient. These stages require specific arrangements for patients with intellectual disability.

Finally, some conditions, especially of genetic origin, are characterized by a **specific response to a treatment**. In Down syndrome, sensitivity to chemotherapy and toxicity of the same treatments vary depending on whether it is a myeloblastic or a lymphoblastic leukemia. This requires therapeutic adjustments [Zeller et al 2005]. Toxicity problems are also encountered in Down syndrome during sarcoma or testicular seminoma treatments [Slavc et al 1991, Grem and Trump 1986]. Increased DNA vulnerability to ionizing radiations accounts for major side effects in the course of cancer treatment in patients with ataxia telangiectasia and in Nijmegen syndrome [Distel et al 2003] as well as in type 1 neurofibromatosis [Gill et al 1999]. Specific anesthetic procedures may also be necessary [Altintas and Cakmakkaya 2004, Altintas and Cakmakkaya 2010]. As in the case for persons of the general population in the terminal phase of cancer, persons with intellectual disability may also be helped and attended to in their last moments. For this purpose, it is necessary to educate teams for the assessment of pain and the monitoring for these specific circumstances [Tuffrey-Wijne 2003].

Conclusion

13. ONCODEFI as a response to the present context

In addition to cancers of childhood, persons with intellectual disability who live longer develop cancer in adulthood and later. As in the general population, and sometimes because of specific factors, cancers are with cardiovascular and respiratory diseases, one of the major causes of death [Janicki et al 2002]. Due to communication difficulties, people with intellectual disability have a lower access to health resources. Diagnosis and treatment are delayed. We must take stock of this new challenge to professionals, health and social institutions, friends and family circles and disabled persons themselves.

Cancers, their prevention, their screening, their treatment are poorly understood by professionals by carers of persons with intellectual disability who are involved in the daily lives of these persons. Furthermore, while disabled children receive, in general, appropriate care, adults with intellectual disability are little understood – sometimes misunderstood – by oncological teams despite individual and institutional good will.

It seems important to us to set up oncological clinical reference teams for cancer in persons with intellectual disability. It seems important to us to regroup for patients, families, healthcare professionals and oncological teams the most relevant documentation in order to tackle cancerous disease right from prevention to the last stages of treatment.

It seems important to us to encourage epidemiological, medico-psychological and biological research work producing results which will help improve, on solid scientific basis, the diagnostic and therapeutic monitoring of persons with intellectual disability. This will reduce the unequal situation of health and loss of chances they face because of their disability.

Such is the vocation of the ONCODEFI project that we have presented here in broad outlines.

Prepared September 2007
Revised February 8th 2012

References

Achtenberg J, Collerrain I, Craig P. A possible relationship between cancer, mental retardation and mental disorders. Soc Sci Med 1978;12:135-9

Al-Saleem T, Wessner LL, Scheithauer BW, Patterson K, Roach ES, Dreyer SJ, Fujikawa K, Bjornsson J, Bernstein J, Henske EP. Malignant tumors of the kidney, brain, and soft tissues in children and young adults with the tuberous sclerosis complex. Cancer 1998;83:2208-16

Altintas F, Cakmakkaya S. Anesthetic management of a child with Rubinstein-Taybi syndrome. Paediatr Anaesth 2004;14:610-1

Altintas F, Cakmakkaya S. Anesthesia in children with intellectual disability. Int J Child Health Hum Develop 2010;3:189-98

Azéma B, Martinez N. Les personnes handicapées vieillissantes: espérances de vie et de santé. Qualité de vie. Revue Française des Affaires Sociales 2005;59:297-333

Bénard J, Béron-Gaillard N, Satgé D. Down's syndrome protects against breast cancer: Is a constitutional cell microenvironment the key? Int J Cancer. 2005;113:168-70

Bishop DT. Genetic predisposition to cancer: an introduction. In: Genetic predisposition to cancer. Eeles EA et al. Ed. 2nd edition Arnold 2004, pp 3-10

Black P, Hyde C. Caring for people with a learning disability, colorectal cancer and stoma. Br J Nurs 2004;13:970-5

Böhmer CJM, Klinkenberg-Knol EC, Niezen-de Boer RC, Meuwissen SGM. The age-related incidences of oesophageal carcinoma in intellectually disabled individuals in institutes in the Netherlands. Eur J Gastroenterol Hepatol 1997;9:589-92

Donaghey V, Bernal J, Tuffrey-Wijne I, Hollins S. Getting on with cancer. London: Gaskell/St. George's Hospital Medical School; 2002

Durkin MS, Hasan ZM, Hasan KZ. Prevalence and correlates of mental retardation among children in Karachi, Pakistan. Am J Epidemiol 1998;147:281-8

Dusart A. Les personnes déficientes intellectuelles face à la mort. Retentissement de la perte d'un proche et fin de vie. Editions de la Fondation de France, 1998

Eng C. Cowden syndrome. In Eeles RA, Easton DF, Ponder BAJ, Eng C: Genetic predisposition to cancer. Arnold 2nd Ed. 2004, pp 155-66

Garcin N. Les définitions et systèmes de classification. In: La déficience intellectuelle Tassé MJ and Morin D. Morin G Ed. 2003, pp 25-37

Gillberg C, Soderstrom H. Learning disability. Lancet 2003;362:811-21

Grem JL, Trump DL. Reversible increase in serum alpha-fetoprotein content associated with hepatic dysfunction during chemotherapy for seminoma. J Clin Oncol 1986;4:41-5

Gripp KW. Tumor predisposition in Costello syndrome. Am J Med Genet C Semin Med Genet 2005;137:72-7

Guillamo JS, Creange A, Kalifa C, Grill J, Rodriguez D, Doz F, Barbarot S, Zerah M, Sanson M, Bastuji-Garin S, Wolkenstein P; Reseau NF France. Prognostic factors of CNS tumours in Neurofibromatosis 1 (NF1): a retrospective study of 104 patients. Brain 2003;126:152-60

Hanna LM, Taggart L, Cousins W. Cancer prevention and health promotion for people with intellectual disabilities: an exploratory study of staff knowledge. J Intellect Disabil Res. 2011;55:281-91

Hasle H, Clemmensen IH, Mikkelsen M. Risks of leukaemia and solid tumours in individuals with Down's syndrome. Lancet 2000;355:165-9

Henderson CM. Genetically –linked syndromes in intellectual disabilities. Journal of Policy Practice in Intellectual Disabilities 2004;1:31-41

Hendren RL, Taylor WS, Lemke BJ, Lemke PA. An autistic boy copes with a terminal illness. J Am Acad Child Adolesc Psychiatry 1990;29:901-4

Hennequin M, Morin C, Feine JS. Pain expression and stimulus localisation in individuals with Down's syndrome. Lancet. 2000;356:1882-7.

Hogg J, Northfield J, Turnbull J. Cancer and People with learning Disabilities: the evidence from published studies and experiences from cancer services. Bild Publications: Kidderminster 2001

Holst K, Andersen E, Philip J, Henningsen I. Antenatal and perinatal conditions correlated to handicap among 4-year-old children. Am J Perinatol 1989;6:258-67

Isaacs H Jr. Etiology and incidence. In: Tumors of the fetus and newborn. WB Saunders Ed. 1997, pp 1-14

Janicki MP, Davidson PW, Henderson CM, McCallion P, Taets JD, Force LT, Sulkes SB, Frangenberg E, Ladrigan PM. Health characteristics and health services utilization in older adults with intellectual disability living in community residences. J Intellect Disabil Res 2001;46:287-98

Jeanpierre M. Déficience mentale: explorations visant au conseil génétique. In Génétique Médicale, formelle, chromosomique, moléculaire, clinique. Masson Ed. 2004, pp 195-208

Jones KL. Mental deficiency approaches. In: Smith's recognizable patterns of human malformation WB Saunders ed 5th ed 1997 pp 681-7

Kiess W, Linderkamp O, Hadorn HB, Haas R. Fetal alcohol syndrome and malignant disease. Eur J Pediatr 1984;143:160-1

Marvis CA, Decoufle P, Murphy CC, Yeargin-Allsopp M. Low birthweight and the risk for mental retardation later in childhood. Paediatr Perinat Epidemiol 1995;9:455-68

Merrick J, Davidson PW, Morad M, Janicki MP, Wexler O, Henderson CM. Older adults with intellectual disability in residential care centers in Israel: health status and service utilization. Am J Ment Retard 2004;109:413-20

Miller RW, Rubinstein JH. Tumors in Rubinstein-Taybi syndrome. Am J Med Genet 1995;56:112-5

Narod SA, Stiller C, Lenoir GM. An estimate of the heritable fraction of childhood cancer. Br J Cancer 1991;63:993-9

O'Brien KF, Tate K, Zaharia ES. Mortality in a large southeastern facility for persons with mental retardation. Am J Ment Retard 1991;95:397-403

Patja K, Eero P, Iivanainen M. Cancer incidence among people with intellectual disability. J Intellect Disabil Res 2001;45:300-7

Primrose DAA. Natural history of mental deficiency in a hospital group and in the community it serves. J Ment Defic Res 1966;10:159-89

Rehder H, Fritz B, Genetic causes of mental retardation. Wien Med Wochenschr 2005;155:258-67

Réthoré M-O. How to talk to children with trisomy 21. Int J Disabil Hum Dev 2006;4:333-6

Sasco AJ, Ah-Song R, MD, Nishi M, Culine S, Réthoré M-O, Satgé D. Testicular cancer and intellectual disability. Int J Disabil Hum Dev 2008;7:397-403

Satgé D, Sommelet D, Geneix A, Nishi M, Malet P, Vekemans M. A tumor profile in Down syndrome. Am J Med Genet 1998;78:207-16

Satgé D, Sasco AJ, Pujol H, Rethore M.-O. Les tumeurs mammaires chez les femmes trisomiques 21. Bull Acad Natl Med 2001;185:1239-54

Satgé D, Sasco AJ. Breast screening guidelines should be adapted in Down's syndrome. Brit Med J 2002;324:1155

Satgé D, Créau N, Aflalo-Rattenbach R, Ducassou S, Lutz P, Bénard J. Down syndrome's protection against neuroblastoma : the stromal and neural overmaturation tracks. In: Andre LH, Roux NE, Eds. Focus on neuroblastoma research, Nova Sciences Publisher New York 2008. pp 57-100

Satgé D, Sasco AJ, Azema B, Culine S. Cancers in persons with intellectual deficiency: current data. In: Mental Retardation Research Focus. Nova Sciences Publisher (New York) 2007 pp 47-84

Satgé D, Bénard J. Carcinogenesis in Down Syndrome; what can be learned from trisomy 21? Sem Cancer Biol 2008;18:365-71

Satgé D, De Lonlay P. A review of neoplasms in persons with intellectual disability related to inherited metabolic disorders. Int J Child Health Hum Dev 2010;3:165-71

Satge D, Merrick J. Cancer in children and adults with intellectual disability: current research. Nova Science Publishers New York 2011

Schultz-Pedersen S, Hasle H, Olsen JH, Friedrich U. Evidence of decreased risk of cancer in individuals with fragile X. Am J Med Genet 2001;103:226-30

Slavc I, Urban C, Haas OA, Kroisel PM, Koller U. Acute megakaryocytic leukemia in children. Clinical, immunologic, and cytogenetic findings in two patients. Cancer 1991;68:2266-72

Strauss D, Shavelle R. Life expectancy of persons with chronic disabilities. J Insur Med 1998;30:96-108

Strauss D, Cable W, Shavelle R. Causes of excess mortality in cerebral palsy. Dev Med Child Neurol 1999;41:580-5

Sugita K, Izumi T, Yamaguchi K, Fukuyama Y, Sato A, Kajita A. Cornelia de Lange syndrome associated with a suprasellar germinoma. Brain Dev 1986;8:541-546

Sullivan SG, Hussain R, Threlfall T, Bittles AH. The incidence of cancer in people with intellectual disabilities. Cancer Causes Control 2004;15:1021-5

Tassé MJ, Morin D. L'étiologie. In: La déficience intellectuelle Tassé MJ, Morin D. Morin G Ed., 2003, pp 25-37

Tracy J, Hosken R. The importance of smoking education and preventative health strategies for people with intellectual disability. J Intel Disabil Res 1997;41:416-21

Tuffrey-Wijne I. The palliative care needs of people with intellectual disabilities: a literature review. Palliat Med 2003;17:55-62

Tuffrey-Wijne I, Bernal J, Jones A, Butler G, Hollins S. People with intellectual disabilities and their need for cancer information. Eur J Oncol Nurs 2006;10:106-16

Tuffrey-Wijne I, Hogg J, Curfs L. End-of-life and palliative care for people with intellectual disabilities who have cancer or other life-limiting illness: a review of the literature and available resources. Journal of Applied Research in Intellectual Disabilities 2007;20:331-44

Tuffrey-Wijne I, Davis J This is my story: I've got cancer. "The Veronica project: an ethnographic study of the experience of people with learning disability whi have cancer. Br J Learning Disab 2007;35:7-11

Tuffrey-Wijne I, Bernal J, Hubert J, Butler G, Hollins S. People with learning disabilities who have cancer: an ethnographic study. Br J Gen Pract. 2009;59:503-9

Tuffrey-Wijne I. Living with learning disabilities, Dying with cancer. Jessica Kingsley Publishers London 2010

Verger P, Aulagnier M, Souville M, Ravaud JF, Lussault PY, Garnier JP, Paraponaris A. Women with disabilities: general practitioners and breast cancer screening. Am J Prev Med 2005;28:215-20

Windham GC, Bjerkedal T, Langmark F. A population-based study of cancer incidence in twins and in children with congenital malformations or low birth weight, Norway, 1967-1980. Am J Epidemiol 1985;121:49-56

Zeller B, Gustafsson G, Forestier E, Abrahamsson J, Clausen N, Heldrup J, Hovi L, Jonmundsson G, Lie SO, Glomstein A, Hasle H; Nordic Society of Paediatric Haematology and Oncology (NOPHO). Acute leukaemia in children with Down syndrome: a population-based Nordic study. Br J Haematol 2005;128:797-804