# Down syndrome today and tomorrow

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Résumé

Le syndrome de Down : aujourd'hui et demain

Le domaine de la trisomie 21 est en pleine évolution. Le suivi médical et les soins de santé sont de plus en plus disponibles. Les techniques comportementales de réhabilitation se précisent et gagnent en

efficacité ; encore faudrait-il qu'elles soient davantage accessibles à toutes les familles concernées dans les divers pays, pas seulement ceux du monde occidental. Les perspectives de pharmacothérapie se précisent également, même si beaucoup de travail reste encore à faire avant de pouvoir disposer de ressources sûres et efficaces dans ce secteur. Les avancées les plus prometteuses, encore à confirmer également, sont relatives aux thérapies génétiques et épigénétiques D'importants progrès ont été rendus possibles en laboratoire ces dernières années grâce à la mise au point et à l'exploitation heuristique de modèles animaux de la trisomie 21. Des applications cliniques au niveau humain sont déjà en cours.

Et au même moment, dans nombre de pays occidentaux, la survie même des bébés diagnostiqués en prénatal comme étant porteurs d'une trisomie 21, est gravement menacée au nom d'un avortement dit thérapeutique légal au cours de la première période de la grossesse.

L'article synthétise les principales informations concernant l'état présent et les avancées qu'on peut raisonnablement espérer dans le domaine pour le futur à court et à moyen terme.

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Abstract

The field of Down syndrome (trisomy 21) is evolving. Medical and health care are more available. Behavioral rehabilitation techniques are made more precise and are gaining in efficiency. Each and every family concerned with the condition, not only those in Western societies, should be able to benefit from these progresses.

Even if we are only at the beginning, the prospect for an efficient cognitive pharmacotherapy is better than a few years ago. Promising perspectives also exist regarding genetic and epigenetic therapeutic approaches. The latter years have witnessed important progresses in research thanks to the creation of animal models of trisomy 21. Clinical applications at the human level have already begun.

And yet, at the same time, in a growing number of Western countries, in particular, the right to be born is denied to fetuses diagnosed with Down syndrome who are aborted within the first months of pregnancy.

The paper summarizes major information regarding the present state of the question and what may be reasonably expected in the near and longer-term future for persons with Down syndrome.

1. Down syndrome

Down syndrome (DS - etiologically trisomy 21 - T21) is the most common cause of cognitive disability with an incidence of approximately one case every 1,000 living births. Prevalence in the world today may be estimated to be around 10 millions people. Life

expectation is close to sixty years and increasing regularly thanks to improved medical care and health programs, family and school education, early stimulation, better psychological development, and social inclusion.

T21 can be partial, complete, or mosaic. Complete T21 comes in two varieties: standard T21, with all the body cells equipped (?) with 47 chromosomes instead of 46 normally due to the triplication of chromosome 21 (93% of the cases); translocation trisomy, whereby the long arm of chromosome 21 or a portion of it agglomerates to another chromosome and reciprocally (5% of the cases). In mosaic cases (2%), only a part of the body cells have T21; the proportion depending on the moment when the nondisjunction or the translocation involving chromosome 21 takes place in early embryonic development.

Chromosome 21 holds approximately 300 genes only a portion of which are directly involved in the phenotype of DS. They are thought to be genes demonstrating dosage sensitivity, i.e., genes that when triplicated express more than 1x their normal protein coding potential resulting in altered proteomics responsible for the pathological features of the condition.

Pathognomonic features of DS are a marked developmental delay in the cognitive domain (language, memory, intellectual functioning), premature aging manifesting itself from the fourth decade of life, and

an increased susceptibility to early Alzheimer pathology in about 15% of the persons.

## 2. The present-day paradox

While the biological and behavioral research is making significant progress that is translatable into specific rehabilitation practice, as I shall document, the very existence of people with DS is in jeopardy in a growing number of countries due to a raising practice of eliminating the fetus diagnosed with trisomy 21 following prenatal screening.

It is now possible to reliably diagnose trisomy 21 through the analysis of a sample of maternal blood as soon as the 10$^{th}$ week of pregnancy. In several Western countries, the available statistics indicate that something like 90-95% of provoked abortions following a diagnosis of DS.  Phrase pas finie ?

Several international declarations (e.g., United Nations, European Community) assert the right of disabled people to be educated to the best of their abilities, to lead a decent life, etc., which, quite obviously, means a right to live in the first place.

Should we blame the parents who following early diagnosis decide to abort the fetus, I do not think so. The right of parents to freely decide, providing that they have been duly and completely informed

on the condition, is unquestionable as well as the right of women to dispose of their own bodies.

However, opposed to this parents' and women's right is the as much inalienable right of any child to be born in the first place and to conduct a decent life. The two rights are contradictory and we would need a God to change the situation.

More earthly, we should be working to convince the States to better support the parents, starting with the parents to be, economically and otherwise in order to render less overwhelmingly difficult the task to raise a child with congenital genetic condition such as DS. As Lionel Penrose once put it (référence ? pas dans la biblio), States should be judged on the basis of what they do in favor of their less favored citizens.

3. Down syndrome today

People with DS, no doubt, are better off today than in the past, particularly the more remote past, which does not render their present-day situation in any way satisfactory.

Thanks to remarkable progresses in medicine, developmental psychology and education, and to dedicated parents raising their handicapped child at home, life expectancy and quality of life have been markedly improved for persons with DS over the last 50 years.

Mean life expectancy was still close to 12 years after the Second World War. It is now around 60 years and increasing regularly. Early help for parents and children with DS are available in a number of economically developed countries. Special schools for the intellectually disabled have been in existence for a long time in our countries. Inclusion schools or classes where the child with DS can be integrated with typically developing (TD) children have been organized in a number of places for several decades now.

And yet much more could be done. For example, at the school level, parents overwhelmingly favor the inclusion of their child in mainstream classes, right from preschool. In some countries, this is not a right but a tolerance or a privilege allowed upon request and easily revocable at the discretion of the school system.

Integrating a child with intellectual disability into a class for TD children is a difficult task both for the teacher and for the disable child. Mainstream teachers are not always prepared for such an additional duty. Without help from an adjunct teacher, they often do not have (?) time enough to meet the needs of a handicapped child integrated in their classes.

Cognitive rehabilitation of the child with DS is now a reality in a number of places. There is no doubt that it is useful. And yet from what I have seen in several counties (admittedly a restricted sample), this type of rehabilitation is most often not intensive or systematic

enough. It is not always optimally timed and therefore less efficient that it could be. Comprehensive rehabilitation programs aimed particularly at children with DS have been proposed in recent years (e.g., a dozen of chapters in a book edited by Rondal & Buckley, 2003; Kumin's 2012 practical intervention manual for language and cognitive development; a series of chapters in a book edited by Rondal & Perera, 2011;Rondal's 2013a, 2013b surveys of rehabilitation techniques in DS).

One of the reasons for this less that optimal state of affairs is a lack of specialized knowledge in many clinicians. Our Universities and high schools should endeavor to train more people in these areas to meet a growing demand.

4. Down syndrome in coming years

One of the next challenges in DS may be to develop an efficient and safe pharmacotherapy to assist cognitive development and rehabilitation. Although Capone (2011), one of the leading experts in the domain, is cautious not overdo the topic nor to raise false hopes in parents and people with DS, it is reasonable, I believe to expect significant advances in this domain in the short- and middle-term future. A list of drugs, some already approved by the U.S. Food and Drug Administration (FDA) seems to hold promises for efficient applications. It is true that many compounds advertised in the media in latter decades (vitamins, hormones, metabolic precursors),

without any sound theory behind and lacking proven mechanism of action, not surprisingly failed to determine lasting effects on cognitive development and functioning in persons with DS.

Some of the new products, such as Donezepil and Rivastigmine, target inhibitory neurotransmitters in the brain, the so-called cholinergic system. This system is defective in adults and aging persons with DS, and possibly also in children. These drugs have proved efficacious in boosting adaptive behavior, memory and language in adults with DS and children.

The primary inhibitory neurotransmitter in the brain is the gamma-aminobutyric acid (GABA) – probably utilized in as many as 40% of cortical synapses. There is in experimental trial a number of drugs designed to modulate GABA receptors which offer promises for helping to alleviate brain interneuron insufficiencies.

Excitatory neurotransmitters in the brain, particularly amino acid glutamate, are also on the researchers' agenda. The hope is to succeed in calibrating drugs able to amplify neural signaling without overstimulation.

An efficient pharmacology of cognitive enhancement is in the pipeline. Safety issues must be dealt with all the most seriously. Timing also is central. Brain development is an exquisitely fine intricacy of events, each with a particular calendar that needs to be

carefully respected. The problem is that the train of neurological events linked to cognitive maturation is not known in sufficient detail which complicates the task of the cognitive pharmacological researcher.

Also present-day and future molecules with the power of boosting cognitive development will need to be utilized for maximal efficiency together with optimized behavioral and educational intervention (Rondal & Perera, 2011).

Something can be said regarding the particular susceptibility of aging persons with DS to develop Alzheimer disease (AD). While there is no cure at this time for AD in persons with or without DS, a small number of prescription drugs have been experimented to treat its symptoms (Florez, 2010) : donezepil, galantamine, rivastigmine, and tarine are cholinesterinase inhibitors. They prevent the breakdown of the inhibitory neurotransmitter acetylcholine in brain synapses. Memantine regulates the activity of glutamate, the primary excitatory neurotransmitter in the brain, also essential for learning and memory. AD damages or destroys cells that produce and use acetylcholine, thereby reducing the amount of neurotransmitter available to carry neuronal messages.

Memantine, already approved by the FDA in 2002, has been revolutionary in transforming AD from a disease for which there was

no pharmacotherapy to a disease for which there is a potential treatment.

The drugs mentioned above provide symptomatic improvement and have a modest impact on the progression of the disease from mild cognitive impairment to disabling dementia, particularly if they are prescribed early in the disease. This raises the question of early diagnosing AD in persons with DS which is becoming feasible utilizing neuropsychological batteries of cognitive and language tests (for example, George et al., 2001).

Some other drugs are currently under investigation (e.g., other cholesterinase inhibitors such as dimebon). This makes it likely that in coming years important new pharmacological options will become available for the treatment of AD.

Moreover, basic research aiming at understanding how AD affects the brain is progressing. A likely culprit is the so-called amyloid cascade.

In DS, the point of departure is found in the overexpression (of ?) the APP gene (amyloid precursor protein) located on chromosome 21, likely in interaction with other genes in the genome that are still the object of discussions. From the first years of life, there is an elevated production of a peptide, amyloid-alpha, in the brain of persons with DS. Amyloid-alpha proteins are nontoxic. A so far unidentified

process is needed for the APP gene to start coding for related peptides, amyloid-bêta 40 and 42, which are not soluble in the brain fluids. These latter peptides are the ones that cause the accumulation of the amyloid plates invading synapses, hence disturbing neurotransmission. Gradually, the amyloid plates circumscribe the neurons which favor the accumulation in the neuron cytoplasm of a protein called Tau that causes a deep alteration of the neuronal cell tissue in the form of neurofibrillation (Zigman et al., 2008).

5. Down syndrome somewhat later

Ambitious in vitro experiments in epigenetic therapy of T21 have been published recently. They hold promises for a possible cure in coming years. Two teams of researchers have succeeded in correcting pluripotent cells affected with T2, transforming them into their disomic counterparts, i.e., cells with the regular number of chromosomes. Pluripotent cells are morphofunctional cells (for example, skin fibroblasts) collected from adult organisms and reprogrammed into cells that can be specialized into a series of other cells (neurons, cardiac tissue, liver cells, etc.) through the action of particular genes (4 in the seminal work of Shynia Yamanaka, 2012 Nobel prize of Medicine and Physiology together with the biologist John Gurdon also a pioneer in stem cells and nuclear reprogrammation).

Li et al. (2012) introduced a particular fusion transgene at the locus of the APP gene using an adenovirus as carrier in one of the three chromosomes 21 in cells obtained from a human person with DS. The result was the silencing or the elimination of the additional chromosome 21 rendering the treated cells disomic. Jiang et al. (2013) performed gene editing, a procedure that allows DNA to be cut and pasted, to drop a gene called XIST into the extra chromosome 21 in cells obtained from a male person with DS. The XIST gene is (a?)no common gene. It is crucial for normal human development. Sex is determined by the combination of X and Y chromosomes that a person inherits. Men are XY and women XX. The XIST gene is located on the X chromosome but it is only active in women. When it switches on, it has the effect of silencing the second X chromosome in women in order to avoid gene surdosage (the X chromosome is bigger and holds more genes than the tiny Y chromosome). The XIST gene silences the second X chromosome by coating it with a particular version of the molecule RNA. Once inserted in the extra chromosome 21 in pluripotent trisomic cells at the locus of the gene DYRK1A, the XIST gene was (is?) able to silence this chromosome in more than 85% of the treated cells, thus rendering them disomic.

These works open new and dramatic perspectives for a genetic cure of DS. Many intermediate steps are still necessary before any prospective application in vivo can be envisaged. In particular, the

safety of the procedures must be ascertained. No human application can be considered before probably several years. The Massachusetts team (Jiang et al.) is already up trying to prevent T21 in early-stage experimental mice embryos with the equivalent of partial trisomy 21 which would correct the developing mouse to a large extent.

We are still far away in humans from experiments of the kind. But it will perhaps be technically possible, ethical and safe some time later. When we will reach that clinical stage, very early diagnosis of DS in humans will be a necessity, becoming then a life improving event and no longer a possible death sentence.

However, the epigenetic improvement of DS does not need to be restricted to chromosomal intervention. Individual genes in the so-called critical area of DS on chromosome 21 (the set of genes that are thought to be involved in causing the typical phenotype of the condition because they are dosage-sensitive). Current work is targeting particular genes and hold promises for improving the developmental prognosis in experimental mice, and as it would seem, also in humans.

Epigallocathechine gallate (EGCG), a green tea polyphenol (a natural antioxidant) appear to have the property of reducing the expression of the gene DYRK1A, involved in neurogenesis. As demonstrated, mice with the equivalent of T21, treated from gestation to adult age, have a cerebrogenesis markedly less altered that their non-treated

peers and close to non-trisomic mice. There are also clear benefits regarding their ability of learning and memory (Delabar, 2011).

EGCG is currently being tested at the human level in several research centers with adolescents with DS. Preliminary data are promising. Few adverse reactions are noted and positive behavioral indications are emerging that dissipate when the treatment is interrupted. This corroborates the efficiency of the product but also attest to symptomatic effects.

Other genes involved in the determinism of the DS phenotype are the targets of other investigations, for example, the CBS gene on chromosome 21 (cystathionine bêta-synthase). This gene, coding for an enzyme, is overexpressed in several brain structures, among which the hippocampus and the cerebellum. The Lejeune Foundation, in Paris, has recently registered a patent for a molecule with an inhibitory action over that CBS gene.

It seems that in the near future it will be possible to start regulating efficiently the action of a number of genes involved in the neurogenesis and cognitive functioning.

Other epigenetic strategies are being defined and searched. Any excess of DNA product induces a corresponding augmentation in messenger RNA, given that the latter carries the DNA instructions outside of the nucleus in the cell cytoplasm where protein

assembling takes place. Some smaller RNA could be used to silence any gene in the human genome.

Another strategy would be to target the gene products, i.e., the proteins coded by the gene, which the domain of proteomics, the science of proteins.

Beyond epigenetic therapy, there is genetic therapy, i.e., acting on the genes themselves, not only regulating their expression or modifying their product. Important progresses have been made in recent years regarding the task of inserting particular replacement or modified genes within the genome of a human being in order to treat pathologies such as type-B haemophilia, the immunity deficiencies linked to the X chromosome, etc. The vectors utilized to deliver the modified or the replacement genes are altered virus, retrovirus or adenovirus. The therapeutic strategy consists in subtracting from the virus its genetic material and replace it with the therapeutic gene. Different viruses have different cell affinities. It is possible to select them according to the type of cell that one wants to reprogram.

All that is not without danger. Our immunity systems have evolved to fight viral aggressions. Genetic viral therapy has to prove safe in the first place.

6. Final considerations

Cognitive pharmacotherapy, epigenetic and genetic therapies are on the way. It will take a few more years and additional research to have them safely applicable in the human clinics. This joined with regularly advancing medical care and intervention for people with DS will considerably change the developmental outcome and life reality of these people; maybe to an extent that we cannot imagine at the present time.

These progresses will render the brain of people with DS more able to learn, memorize and behave in more sophisticated ways. However, cognitive intervention and education will always be necessary, if only because, so to speak, brain sciences, neurological, pharmacological, or genetical, pertain to the hardware while the software is behavioral. It follows that behavioral intervention is not in competition with more biologically motivated approaches. The task ahead is to combine the therapeutic approaches, biological and behavioral, so as to promote a better development and functioning in persons with DS.

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